

PCT/EP 97/07011

08/856,533

REC'D 03 MAR 1998

WIPO

PCT

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME;

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

PRIORITY DOCUMENT

January 26, 1998

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 08/856,533

FILING DATE: May 14, 1997

IP AUSTRALIA

24 JUN 1998

RECEIVED



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. R. GRANT

Certifying Officer

ATTORNEY DOCKET NUMBER: 6013-192-999
SERIAL NUMBER: 09/674,877
REFERENCE: BB

68348 U.S. PTO
08/856533
08/14/97

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

23/1997 MFL078 00000041 08856533
FC:101 770.00 00

PTO-1556
(5/87)

SOLID AND SOLUTION PHASE SYNTHESIS OF EPOTHILONES A AND B AND LIBRARIES OF EPOTHILONE ANALOGS

Specification

Technical Field of the Invention:

The present invention relates to epothilone A, epothilone B, epothilone analogs, libraries of epothilone analogs, and methods for producing such compounds using solid phase and solution phase chemistries.

Government Rights:

This invention was made with government support under Grants No. CA 6446 and CA 58336 awarded by the National Institutes of Health. The U.S. government has certain rights in the invention.

Background of the Invention:

Epothilone A (1, Figure 1) and epothilone B (2, Figure 1) are natural substances isolated from myxobacteria Sorangium cellulosum strain 90. These natural substances exhibit cytotoxicity against taxol-resistant tumor cells and may prove to have a clinical utility comparable or superior to Taxol. (For Taxol references see: Horwitz et al. Nature 277, 665-667 (1979); Nicolaou et al. Angew. Chem. Int. Ed. Engl. 33, 15-44 (1994).) Like taxol, the epothilones are thought to exert their cytotoxicity by induction of microtubule assembly and stabilization. (Bollag et al. Cancer Res. 55, 2325-2333 (1995); Kowalski et al. J. Biol. Chem. 272, 2534-2541 (1997).) Epothilones are reported to be about 2000-5000 times more potent

than Taxol with respect to the stabilization of microtubules. Despite the marked structural differences between the epothilones and TaxolTM, the epothilones were found to bind to the same region on microtubules and to displace TaxolTM from its binding site. (Grever et al. Seminars in Oncology 1992, 19, 622-638; Bollag et al. Cancer Res. 1995, 55, 2325-2333; Kowalski et al. J. Biol. Chem. 1997, 272, 2534-2541; Horwitz et al. Nature 1979, 277, 665-667; Nicolaou et al. Angew. Chem. Int. Ed. Engl. 1994, 33, 15-44.) Epothilones A and B have generated intense interest amongst chemists, biologists and clinicians due to their novel molecular architecture, important biological action and intriguing mechanism of action. (Höfle et al. Angew. Chem. Int. Ed. Engl. 35, 1567-1569 (1996); Grever et al. Semin. Oncol. 19, 622-638 (1992); Bollag et al. Cancer Res. 55, 2325-2333, (1995); Kowalski et al. J. Biol. Chem. 272, 2534-2541 (1997); Nicolaou et al. Angew. Chem. Int. Ed. Engl. 35, 2399-2401 (1996); Meng et al. J. Org. Chem. 61, 7998-7999 (1996); Bertinato et al. J. Org. Chem. 61, 8000-8001 (1996); Schinzer et al. Chem. Eur. J. 2, 1477-1482 (1996); Mulzer et al. Tetrahedron Lett. 37, 9179-9182 (1996); Claus et al. Tetrahedron Lett. 38, 1359-1362 (1997); Gabriel et al. Tetrahedron Lett. 38, 1363-1366 (1997); Balog et al. Angew. Chem. Int. Ed. Engl. 35, 2801-2803 (1996); Yang et al. Angew. Chem. Int. Ed. Engl. 36, 166-168 (1997); Nicolaou et al. Angew. Chem. Int. Ed. Engl. 36, 525-527 (1997); Schinzer et al. Angew. Chem. Int. Ed. Engl. 36, 523-524 (1997); Meng et al. J. Am. Chem. Soc. 119, 2733-2734 (1997).)

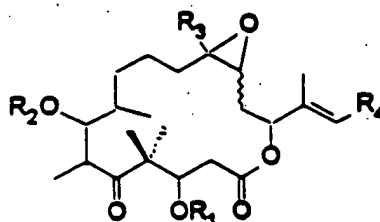
What is needed are analogs of epothilone A and B and libraries of analogs of epothilone A and B that exhibit superior pharmacological properties in the area of microtubule stabilizing

agents.

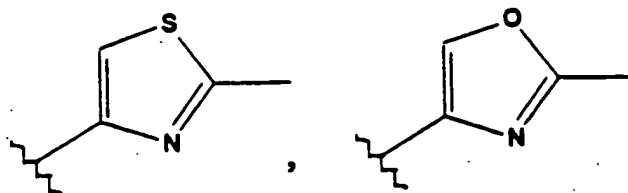
What is needed are methods for producing synthetic epothilone A, epothilone B, analogs of epothilone A and B, and libraries of epothilone analogs, including epothilone analogs possessing both optimum levels of microtubule stabilizing effects and cytotoxicity.

Brief Summary of the Invention:

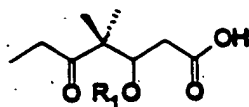
A first mode of the invention is directed to a macrolactonization procedure for synthesizing epothilone and epothilone analogs represented by the following structure:



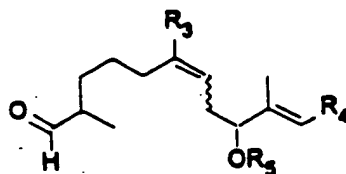
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:



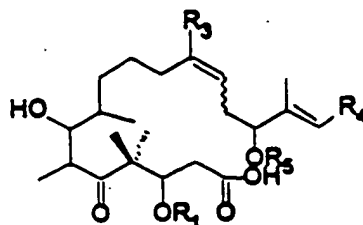
The synthesis may be initiated by condensing a keto acid represented by the following structure:



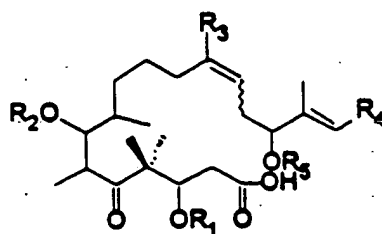
with an aldehyde represented by the following structure:



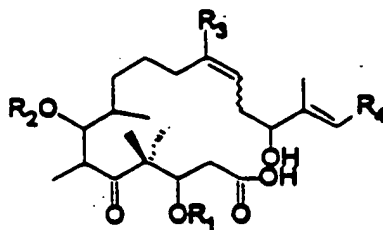
- 10 wherein R₁ is selected from the group consisting of tert-butyltrimethylsilyl and trimethylsilyl, for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:



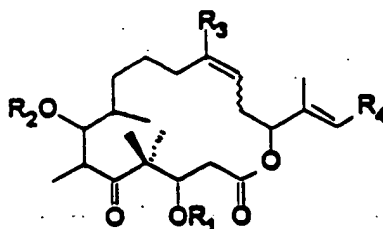
The synthesis is then continued by derivatizing the free hydroxyl moiety of the above carboxylic acid with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:



The R_2 protected hydroxyl moiety of the above derivatized carboxylic acid is then regioselectively deprotected for producing a hydroxy acid with the following structure:



The above hydroxy acid is then macrolactonized for producing a macrolide with the following structure:

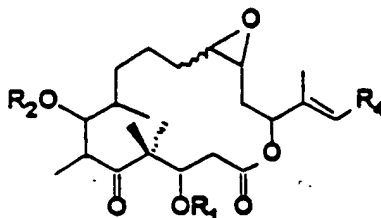


5

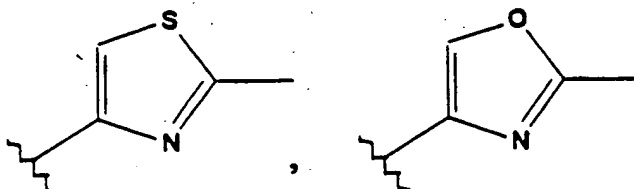
The synthesis is then completed by epoxidizing the above macrolide for producing the epothilone or epothilone analog.

Further aspects of the invention related to this first mode
 10 are directed to each of the individual steps of the above
 synthetic macrolactonization procedure and to each of the
 chemical intermediates employed therein.

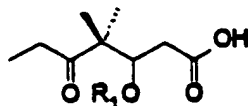
A second mode of the invention is directed to a metathesis
 15 approach to synthesizing epothilone and epothilone analogs
 represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:



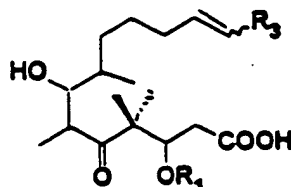
The synthetic protocol is initiated by condensing a keto acid represented by the following structure:



with an aldehyde represented by the following structure:

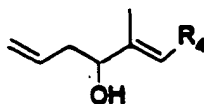


wherein R₃ is selected from the group consisting of hydrogen and (CH₂)_n-(solid phase support), for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:

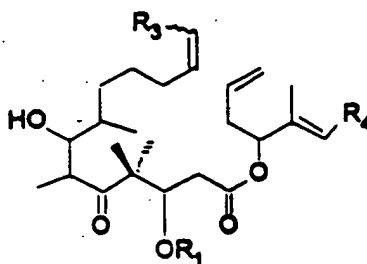


Alternative preferred solid supports include Merrifield resin, PEG-polystyrene, hydroxymethyl polystyrene, formyl polystyrene, aminomethyl polystyrene, and phenolic polystyrene.

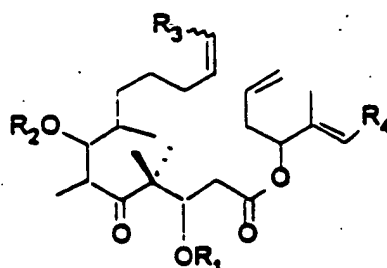
The above carboxylic acid is then esterified with a secondary alcohol represented by the following structure:



for producing an ester with a free hydroxyl moiety represented by the following structure:

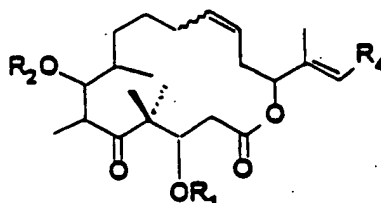


The synthesis is then continued by derivatizing the free hydroxyl moiety of the above ester with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized ester represented by the following structure:



The above derivatized ester is then metathesized with an

organo-metallic catalyst for producing a macrolide with the following structure:

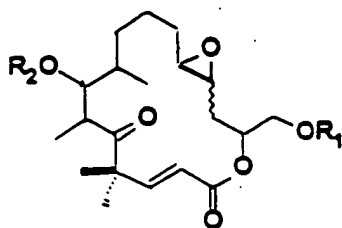


Preferred organo-metallic catalyst include bis(tricyclohexylphosphine)benzylidene ruthenium dichloride and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

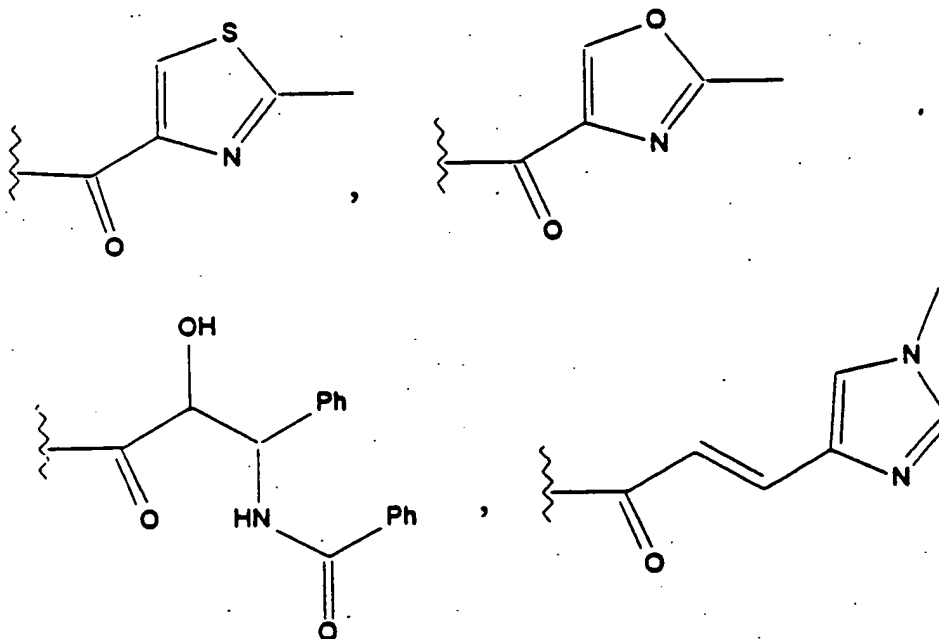
The above macrolide is then epoxidized for producing the epothilone analog.

Further aspects of the invention related to this second mode are directed to each of the individual steps of the above synthetic metathesis procedure and to each of the chemical intermediates employed therein.

A third mode of the invention is directed to a metathesis approach to synthesizing an epothilone analog represented by the following structure:

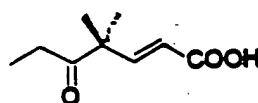


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:

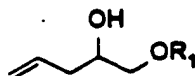


and wherein R_2 is selected from the group consisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl.

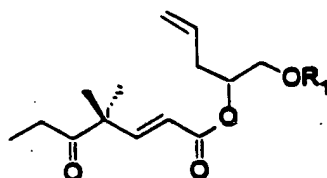
The synthesis is initiated by esterifying a keto acid represented by the following structure:



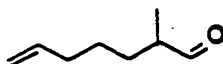
with an alcohol represented by the following structure:



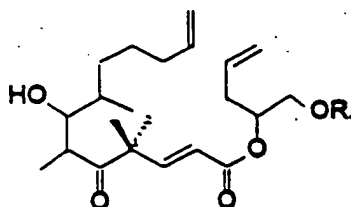
for producing an ester represented by the following structure:



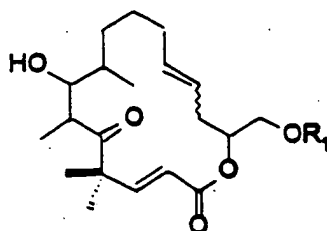
5 Then, the above ester is condensed with an aldehyde represented by the following structure:



for producing a bis-terminal olefin with the following structure:



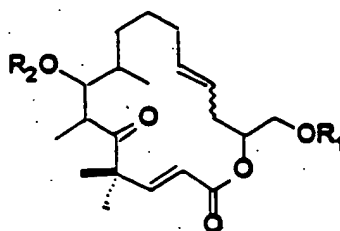
The synthesis is then continued by metathesizing the above bis-terminal olefin with an organo-metallic catalyst for producing a macrocyclic lactone with a free hydroxyl moiety represented by the following structure:



Preferred organo-metallic catalysts include bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

The free hydroxyl of the above macrocyclic lactone is then derivatized with a derivatizing agent represented by the formula

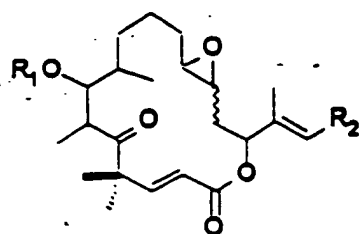
R_2-X wherein R_2-X is selected from the group consisting of hydrogen, tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxymino)-2-phenylacetonitrile for producing a derivatized macrolide with the following structure:



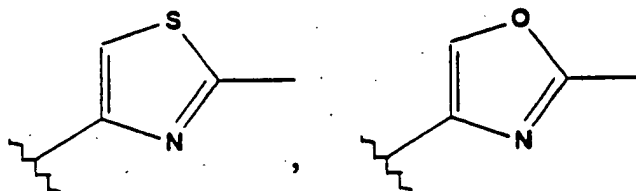
The synthesis is then completed by epoxidizing the above derivatized macrolide for producing the epothilone analog.

Further aspects of the invention related to this third mode are directed to each of the individual steps of the above synthetic metathesis procedure and to each of the chemical intermediates employed therein.

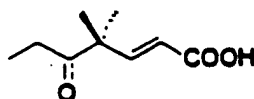
A fourth mode of the invention is directed to a method employing a metathesis approach for synthesizing an epothilone analog represented by the following structure:



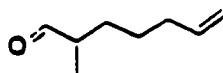
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group represented by the following structures:



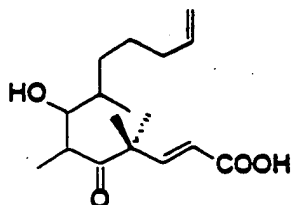
The synthesis is initiated by condensing a keto acid represented by the following structure:



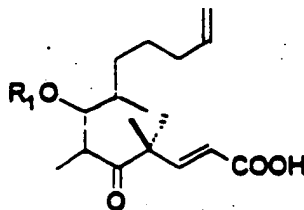
with an aldehyde represented by the following structure:



for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:

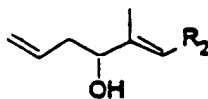


The free hydroxyl moiety of the above carboxylic acid is then derivatized with a derivatizing agent represented by the formula R_1-X wherein R_1-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:

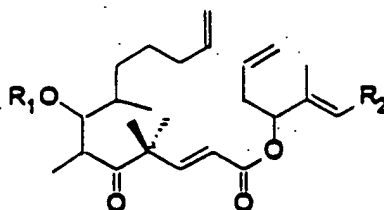


The synthesis is then continued by esterifying the

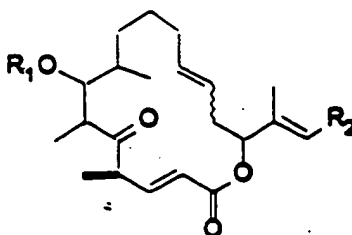
derivatized carboxylic acid of said Step B with an alcohol represented by the following structure:



for producing a bis-terminal olefin with the following structure:



The above bis-terminal olefin is then metathesized with an organo-metallic catalyst for producing a macrocyclic lactone with the following structure:



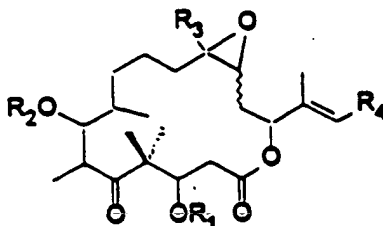
Preferred organo-metallic catalysts include

bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

The synthesis is then completed by epoxidizing the above macrocyclic lactone for producing the epothilone analog.

Further aspects of the invention related to this fourth mode are directed to each of the individual steps of the above synthetic metathesis procedure and to each of the chemical intermediates employed therein.

A fifth mode of the invention is directed to a method employing a macrolatonization approach for synthesizing an epothilone analog represented by the following structure:

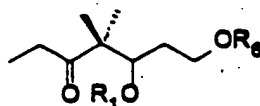


wherein R₁ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R₂ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R₃ is selected from the group consisting of hydrogen, methyl, -CH₂OH,

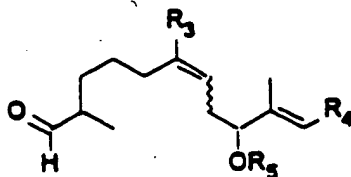
$-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:



The synthesis is initiated by condensing a keto acid represented by the following structure:

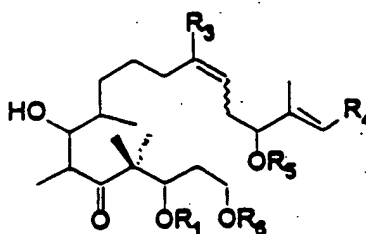


wherein R_1 is selected from the group consisting of tert-butyldimethylsilyl, trimethylsilyl, tert-butyldiphenylsilyl, methyl, hydrogen, triethylsilyl, and benzyl; with an aldehyde represented by the following structure:

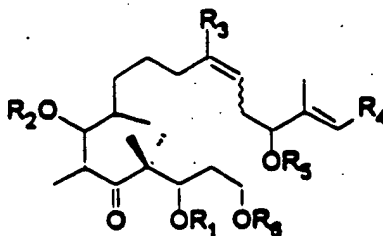


wherein R_2 is selected from the group consisting of tert-

butyldimethylsilyl and trimethylsilyl, for producing a β -hydroxy ketone with a free hydroxyl moiety and a R_4 protected hydroxyl moiety represented by the following structure:

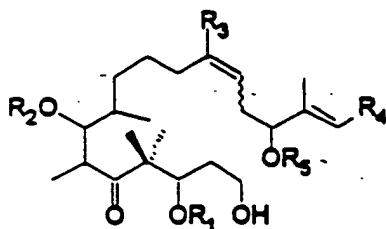


The free hydroxyl moiety of the above β -hydroxy ketone is then derivatized with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized β -hydroxy ketone represented by the following structure:

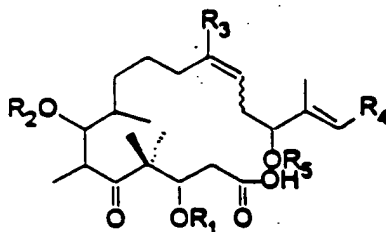


The R_4 protected hydroxyl moiety of the above derivatized β -

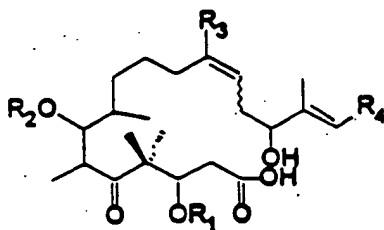
hydroxy ketone is then regioselectively deprotected for producing a terminal alcohol with the following structure:



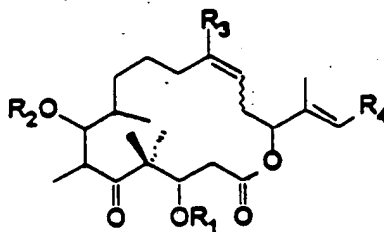
The above terminal alcohol is then oxidized for producing a derivatized carboxylic acid with a R₃ protected hydroxyl moiety with the following structure:



The synthesis is then continued by regioselectively deprotecting the R₃ protected hydroxyl moiety of the derivatized carboxylic acid of said step D for producing a hydroxy acid with the following structure:



The above hydroxy acid is then macrolactonized for producing a macrolide with the following structure:



The synthesis is then completed by epoxidizing the above macrolide for producing the epothilone analog.

Further aspects of the invention related to this fifth mode
 10 are directed to each of the individual steps of the above
 synthetic macrolactonization procedure and to each of the
 chemical intermediates employed therein.

A sixth mode of the invention is directed to the use of each
 15 of the above metathesis approaches for synthesizing libraries of
 epothilone analogs. In this mode, a combinatorial approach is
 employed for synthesizing libraries of epothilone analogs having

various combinations of the preferred R groups.

various combinations of the preferred R groups.

Description of Figures:

Figure 1 illustrates the structure and numbering of epothilone A (1) and B (2).

Figure 2 illustrates the retrosynthetic analysis of the natural product compound epothilone A (1).

Figure 3 illustrates the synthesis of 3 building block substrates wherein A) represents the synthesis of aldehyde 7 with reagents and conditions as follows: (a) 1.05 equivalents of NaHMDS, 2.0 equivalents of *n*-C₅H₉I, 3.0 equivalents HMPA, -78 to 25°C, 5 hours; (b) 1.1 equivalents of LiAlH₄, THF, -78°C, 15 minutes, 60% (2 steps); (c) 1.5 equivalents of NMO, 5 mol % of TPAP, Methylene chloride, 4 Å MS, 25°C, 0.5 hour, 95%. NaHMDS = sodium bis(trimethylsilyl)amide; HMPA = hexamethylphosphoramide, NMO = 4-methylmorpholine-*N*-oxide; TPAP = tetrapropyl ammonium perruthenate; B) represents the synthesis of alcohols 18a and 18b. Reagents and conditions: (a) 1.3 equivalents of TPSCl, 2.0 equivalents of imidazole, DMF, 0 to 25°C, 1.5 hours (90% of 17a, 94% of 17b); (b) 1.25 equivalents of tetravinyltin, 5.0 equivalents of *n*-BuLi, THF, -78°C, 45 minutes, then 2.5 equivalents of CuCN in THF, -78 to -30°C; then 17a or 17b in THF, -30°C, 1 hour, 18a (86%), 18b (83%) (TPS - *n*-Bu₄); C) represents the synthesis of ketoacid 21. Reagents and conditions: (a) 1.2 equivalents of *n*-BuLi, 1.6 equivalents of NaH,

THF, 0 - 25°C, 1 hour, 99%; (b) CF₃COOH:Methylene chloride (1:1), 25°C, 0.5 hour, 99%.

Figure 4 illustrates the synthesis of the epothilone cyclic framework via olefin metathesis: the 15S series. Reagents and conditions: (a) 1.2 equivalents of EDC, 0.1 equivalent of 4-DMAP, Methylene chloride, 0 - 25°C, 12 hours, 86%; (b) 21, 1.2 equivalents of LDA, -78°C - -40°C, THF, 45 minutes; then 1.6 equivalents of 7 in THF, -78 - -40°C, 0.5 hour, 23 (42%), 24 (33%); (c) 0.1 equivalent of RuCl₂(=CHPh)(PCy₃)₂, Methylene chloride, 25°C, 12 hours, 25 (85%), 26 (79%); (d) 2.0 equivalents of TBAF, 5.0 equivalents of AcOH, 25°C, 36 hours, 27 (92%), 28 (95%). DCC = dicyclohexylcarbodiimide, 4-DMAP = 4-dimethylaminopyridine, LDA = lithium diisopropylamide.

Figure 5 illustrates the synthesis of the epothilone cyclic framework via olefin metathesis: the 15R series. Reagents and conditions: (a) 1.4 equivalents of DCC, 1.4 equivalents of 4-DMAP, toluene, 25°C, 12 hours, 95%; (b) 21, 1.2 equivalents of LDA, -78°C - -40°C, THF, 45 minutes; then 1.6 equivalents of 7 in THF, -78 - -40°C, 0.5 hour, 29 (54%), 30 (24%); (c) 0.1 equivalent of RuCl₂(=CHPh)(PCy₃)₂, Methylene chloride, 25°C, 12 hours, 31 (80%), 32 (81%).

Figure 6 illustrates the metathesis approach and epoxidation in the presence of thiazole: synthesis of epothilone analogs 39-44. Metathesis and epoxidation in the presence of thiazole: synthesis of epothilone analogs 39-44. Reagents and conditions:

(a) 21, 2.3 equivalents of LDA, -78 - -30°C, THF, 1.5 hours; then 1.6 equivalents of 7 in THF, -78 - -40°C, 1 hour (33:34, 2:3); (b) ca 2.0 equivalents of 6, ca 1.2 equivalents of EDC, ca 0.1 equivalent of 4-DMAP, Methylene chloride, 0 - 25°C, 12 hours, 35 (29%), 6 (44%) (2 steps); (c) 0.1 equivalent of $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$, Methylene chloride, 25°C, 12 hours, 7 (86%), 38 (66%); (d) 0.9-1.2 equivalents of mCPBA, CHCl_3 , -20 - 0°C, 12 hours, 37 - 39 (or 40) (40%), 40 (or 39) (25%), 41 (18%); 38 - 42 (or 43) (22%), 43 (or 42) (11%), 44 (7%); (e) excess of CF_3COCH_3 , 8.0 equivalents of NaHCO_3 , 5.0 equivalents of Oxone®, $\text{CH}_3\text{CN}/\text{Na}_2\text{EDTA}$ (2:1), 0°C, 37 - 39 (or 40) (45%), 40 (or 39) (28%); 38 - 42 (or 43) (60%), 43 (or 42) (15%). mCPBA = meta-Chloroperbenzoic acid.

Figure 7 illustrates the coupling of building blocks 6-8. Reagents and conditions: (a) 8, 2.3 equivalents of LDA, -78 - -30°C, THF, 1.5 hours; then 1.6 equivalents of 7 in THF, -78 - -40°C, 1 hour (45:46, 3:2); (b) ca 2.0 equivalents of 6, ca 1.2 equivalents of EDC, ca 0.1 equivalent of 4-DMAP, Methylene chloride, 0 - 25°C, 12 hours, 4 (52%), 47 (31%) (2 steps).

Figure 8 illustrates the epoxidation of epothilone framework: total synthesis of epothilone A (1) and analogs 51-57. Epoxidation of epothilone framework: total synthesis of epothilone A (1) and analogs 51-57. (a) 0.1 equivalent of $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$, Methylene chloride, 25°C, 20 hours, 3 (46%), 48 (39%); (b) 20% CF_3COOH in Methylene chloride, 0°C, 3 hours, 3 - 49 (90%); 48 - 50 (92%); (c) 0.8-1.2 equivalents of mCPBA,

CHCl₃, -20 - 0°C, 12 hours, 49 - 1 (35%), 51 (13%), 52 (or 53) (9%), 53 (or 52) (7%), 54 (or 55) (5%), 55 (or 54) (5%); 1 - 54 (or 55) (35%), 55 (or 54) (33%), 57 (6%); (d) 1.3-2.0 equivalents of mCPBA, CHCl₃, -20 - 0°C, 12 hours, 1 (15%), 51 (10%), 52 (or 53) (10%), 53 (or 52) (8%), 54 (or 55) (8%), 55 (or 54) (7%), 56 (5%), 57 (5%); (e) 1.0 equivalent of dimethyldioxirane, CH₂Cl₂/acetone, 0°C, 1 (50%), 51 (15%), 52 (or 53) (5%), 53 (or 52) (5%); (f) excess of CF₃COCH₃, 8.0 equivalents of NaHCO₃, 5.0 equivalents of Oxone®, CH₃CN/Na₂EDTA (2:1), 0°C, 1 (62%), 51 (13%).

Figure 9 illustrates the synthesis of epothilones 58-60. Reagents and conditions: (a) 0.9-1.3 equivalents of mCPBA, CHCl₃, -20 - 0°C, 12 hours, 58 (or 59) (5%), 59 (or 58) (5%), 60 (60%); (b) 1.0 equivalent of dimethyldioxirane, Methylene chloride/acetone, 0°C, 58 (or 59) (10%), 59 (or 58) (10%), 60 (40%); (c) excess of CF₃COCH₃, 8.0 equivalents of NaHCO₃, 5.0 equivalents of Oxone®, MeCN/Na₂EDTA (2:1), 0°C, 58 (or 59) (45%), 59 (or 58) (35%).

Figure 10 illustrates the synthesis of epothilones 64-69. (a) 20% CF₃COOH in Methylene chloride, 0°C, 3 hours, 90%; (b) 0.1 equivalent of RuCl₂(=CHPh)(PCy₃), Methylene chloride, 25°C, 20 hours, 62 (20%), 63 (69%); (c) 0.8-1.2 equivalents of mCPBA, CHCl₃, -20 - 0°C, 12 hours, 62 - 64 (or 65) (25%), 65 (or 64) (23%); 63 - 67 (or 68) (24%), 68 (or 67) (19%), 69 (31%); (d) excess of CF₃COCH₃, 8.0 equivalents of NaHCO₃, 5.0 equivalents of Oxone®, CH₃CN/Na₂EDTA (2:1), 0°C, 62 - 64 (or 65) (58%), 65 (or 64) (29%); 63 - 67 (or 68) (44%), 68 (or 67) (21%).

Figure 11 illustrates the molecular structures and retrosynthetic analysis of epothilones A (1) and B (2) using the macrolactonization approach.

Figure 12 illustrates the synthesis of 2 building block substrates wherein A) represents the synthesis of keto acid 76. Reagents and conditions: (a) 1.2 equivalents of (+)-Ipc₂B(allyl), Et₂O, -100°C, 0.5 hour, 74% (ee >98% by Mosher ester analysis); (b) 1.1 equivalents TBSOTf, 1.2 equivalents of 2,6-lutidine, Methylene chloride, 25°C, 98% ; (c) O₃, Methylene chloride, -78°C, 0.5 hour; then 1.2 equivalents Ph₃P, -78 - 25°C, 1 hour, 90%; (d) 3.0 equivalents of NaClO₂, 4.0 equivalents of 2-methyl-2-butene, 1.5 equivalents of NaH₂PO₄, tBuOH:H₂O (5:1), 25°C, 2 hours, 93%; B) represents the synthesis of phosphonium salt 79 and aldehyde 82. Reagents and conditions: (a) 1.6 equivalents of DIBAL, Methylene chloride, -78°C, 2 hours, 90%; (b) Ph₃P=C(CH₃)CHO, benzene, reflux, 98%; (c) 1.5 equivalents of (+)-Ipc₂B(allyl), Et₂O, -100°C, 0.5 hour, 96% (ee >97% by Mosher ester analysis); (d) 1.2 equivalents TBSCl, 1.5 equivalents of imidazole, DMF, 0 - 25°C, 2 hours, 99%; (e) i. 1.0 mol % OsO₄, 1.1 equivalents of 4-methylmorpholine N-oxide (NMO), THF:tBuOH:H₂O (1 : 1 : 0.1), 0 - 25°C, 12 hours, 95%; ii. 1.3 equivalents of Pb(OAc)₂, EtOAc, 0°C, 0.5 hour, 98%; (f) 2.5 equivalents of NaBH₄, MeOH, 0°C, 15 minutes, 96%; (g) 1.5 equivalents of I₂, 3.0 equivalents of imidazole, 1.5 equivalents of Ph₃P, Et₂O:MeCN (3 : 1), 0°C, 0.5 hour, 89%; g. 1.1 equivalents Ph₃P, neat, 100°C, 2 hours, 98%.

Figure 13 illustrates the synthesis of aldehyde (d) and

ketone 78. Reagents and conditions: (a) 1.1 equivalents of LDA, THF, 0°C, 8 hours; then 1.5 equivalents of 4-iodo-1-benzyloxybutane in THF, at -100 - 0°C, 6 hours, 92% (de >98% by ¹H NMR); (b) O₃, Methylene chloride, -78°C, 77% or MeI, 60°C, 5 hours; then 3 N aq HCl, *n*-pentane, 25°C, 1 hour, 86%; (c) 3.0 equivalents of NaBH₄, MeOH, 0°C, 15 minutes, 98%; (d) 1.5 equivalents of TBSCl, 2.0 equivalents of Et₃N, Methylene chloride, 0 - 25°C, 12 hours, 95%; (e) H₂, Pd(OH)₂ cat., THF, 50 psi, 25°C, 15 minutes, 95%; (f) 2.0 equivalents of (COCl)₂, 4.0 equivalents of DMSO, 6.0 equivalents of Et₃N, Methylene chloride, -78 - 0°C, 1.5 hours, 98%; (g) 1.5 equivalents of MeMgBr, THF, 0°C, 15 minutes, 84%; (h) 1.5 equivalents of NMO, 0.05 equivalent of tetra-*i*-propylammonium perruthenate (TPAP), 4Å MS, Methylene chloride, 25°C, 45 minutes, 96%.

Figure 14 illustrates the total synthesis of epothilone A (1) and its 6*S*,7*R*-diastereoisomers (111 and 112). Reagents and conditions: (a) 1.2 equivalents of 79, 1.2 equivalents of NaHMDS, THF, 0°C, 15 minutes, then add 1.0 equivalent of aldehyde 77, 0°C, 15 minutes, 77% (*Z* : *E* ca. 9 : 1); (b) 1.0 equivalent of CSA portionwise over 1 hour, Methylene chloride:MeOH (1 : 1), 0 - 25°C, 0.5 hour, 86%; (c) 2.0 equivalents of SO₃.pyr., 10.0 equivalents of DMSO, 5.0 equivalents of Et₃N, Methylene chloride, 25°C, 0.5 hour, 94%; (d) 3.0 equivalents of LDA, THF, 0°C, 15 minutes; then 1.2 equivalents of 76 in THF, -78 - -40°C, 0.5 hour; then 1.0 equivalent of 74 in THF at -78°C, high yield of 103a and its 6*S*,7*R*-diastereoisomer 103b (ca. 1 : 1 ratio); (e) 3.0 equivalents of TBSOTf, 5.0 equivalents of 2,6-lutidine, Methylene chloride, 0°C, 2 hours; (f) 2.0 equivalents of K₂CO₃,

MeOH, 25°C, 15 minutes, 31% of 105 and 30% of 6S,7R-diastereoisomer 106 from 74; (g) 6.0 equivalents of TBAF, THF, 25°C, 8 hours, 78%; (h) same as g, 82%; (i) 5.0 equivalents of 2,4,6-trichlorobenzoylchloride, 6.0 equivalents of Et₃N, THF, 25°C, 15 minutes; then add to a solution of 10.0 equivalents of 4-DMAP in toluene (0.002 M based on 72), 25°C, 0.5 hour, 90%; (j) same as i, 85%; (k) 20% CF₃COOH (by volume) in Methylene chloride, 0°C, 1 hour, 92%; (l) same as k, 95%; (m) methyl(trifluoromethyl)dioxirane, MeCN, 0°C, 75% (ca 5:1 ratio of diastereoisomers); (n) same as m, 87% (111 : 112 ca 2 : 1 ratio of diastereoisomers, tentative stereochemistry).

Figure 15 illustrates the synthesis of compound 101. Reagents and conditions: (a) 1.5 equivalents of I₂, 3.0 equivalents of imidazole, 1.5 equivalents of Ph₃P, Et₂O:MeCN (3 : 1), 0°C, 0.5 hour, 91%; (b) 1.1 equivalents Ph₃P, neat, 100°C, 2 hours, 91%; (c) 1.2 equivalents of 114, 1.2 equivalents of NaHMDS, THF, 0°C, 15 minutes; then add 1.0 equivalent of aldehyde 82, 0°C, 15 minutes, 69% (Z : E ca 9 : 1).

Figure 16 illustrates the total synthesis of epothilone B (2) and analogs. Reagents and conditions: (a) 1.5 equivalents of 79, 1.5 equivalents of NaHMDS, THF, 0°C, 15 minutes, then add 1.0 equivalent of ketone 78, -20°C, 12 hours, 73% (Z : E ca 1 : 1); (b) 1.0 equivalent of CSA portionwise over 1 hour, Methylene chloride:MeOH (1 : 1), 0°C; then 25°C, 0.5 hour, 97%; (c) 2.0 equivalents of SO₃.pyr., 10.0 equivalents of DMSO, 5.0 equivalents of Et₃N, Methylene chloride, 25°C, 0.5 hour, 95%; 3.0 equivalents of LDA, THF, 0°C, 15 minutes; then 1.2

equivalents of 76 in THF, -78°C , 0.5 hour; then 1.0 equivalent of 75' in THF at -78°C , high yield of 117a' and its 6S,7R-diastereoisomer 117b' (ca 1 : 1 ratio); (e) 3.0 equivalents of TBSOTf, 5.0 equivalents of 2,6-lutidine, Methylene chloride, 0°C , 2 hours; (f) 2.0 equivalents of K_2CO_3 , MeOH, 25°C , 15 minutes, 31% of 119' and 30% of 6S,7R-diastereoisomer 120' from 75'; (g) 6.0 equivalents of TBAF, THF, 25°C , 8 hours, 75%; (h) 1.3 equivalents of 2,4,6-trichlorobenzoylchloride, 2.2 equivalents of Et₃N, THF, 0°C , 1 hour; then add to a solution of 10.0 equivalents of 4-DMAP in toluene (0.002 M based on 73'), 25°C , 12 hours, 37% of 121; and 40% of 122; (i) 20% CF_3COOH (by volume) in Methylene chloride, $-10 - 0^{\circ}\text{C}$, 1 hour, 91%; (j) same as i, 89%; (k) dimethyldioxirane, Methylene chloride, -50°C , 75% (2 : 124 ca 5 : 1 ratio of diastereoisomers) or 1.5 equivalents of mCPBA, benzene, 3°C , 2 hours, 66% (2 : 124 ca 5 : 1 ratio of diastereoisomers) or methyl(trifluoromethyl)dioxirane, MeCN, 0°C , 85% (2 : 124 ca 5 : 1 ratio of diastereoisomers); (l) 1.5 equivalents mCPBA, benzene, 3°C , 2 hours, 73% (125 : 126 ca 4 : 1 ratio of stereoisomers) or methyl(trifluoromethyl)dioxirane, MeCN, 0°C , 86% (125 : 126 ca 1 : 1 ratio of diastereoisomers).

Figure 17 illustrates the stereoselective synthesis of aldehyde 75 for epothilone B (2). Reagents and conditions: (a) 1.5 equivalents of 83, benzene, reflux, 5 hours, 95%; (b) 3.0 equivalents of DIBAL, Methylene chloride, -78°C , 2 hours, 98%; (c) 2.0 equivalents of Ph_3P , CCl_4 , reflux, 24 hours, 83%; (d) 2.0 equivalents of LiEt_3BH , THF, 0°C , 1 hour, 99%; (e) 1.2 equivalents of 9-BBN, THF, 0°C , 2 hours, 91%; (f) 3.0 equivalents of 1, 3.0 equivalents of imidazole, 1.5 equivalents

of Ph_3P , $\text{Et}_2\text{O}:\text{MeCN}$ (3 : 1), 0°C , 0.5 hour, 92%; (g) 1.5 equivalents of 80, 1.5 equivalents of LDA, THF, 0°C , 8 hours; then 1.0 equivalent of 81 in THF, $-100 - -20^\circ\text{C}$, 10 hours, 70%; (h) 2.5 equivalents of monoperoxyphthalic acid, magnesium salt (MMPP), $\text{MeOH}:\text{phosphate buffer pH7}$ (1:1), 0°C , 1 hour, 80%; (i) 2.0 equivalents DIBAL, toluene, -78°C , 1 hour, 82%.

Figure 18 illustrates the first stereoselective total synthesis of epothilone B (2). Reagents and conditions: (a) 3.0 equivalents of LDA, THF, 0°C , 15 minutes; then 1.2 equivalents of 76 in THF, $-78 - -40^\circ\text{C}$, 0.5 hour, then 1.0 equivalent of 75 in THF at -78°C , high yield of 117a and 6*S*,7*R*-diastereoisomer 117b (ca 1.3 : 1.0 ratio of diastereoisomers); (b) 3.0 equivalents of TBSOTf, 5.0 equivalents of 2,6-lutidine, Methylene chloride, 0°C , 2 hours; (c) 2.0 equivalents of K_2CO_3 , MeOH, 25°C , 15 minutes, 32% of 119 and 28% of 6*S*,7*R*-diastereoisomer 119 from 75; (d) 6.0 equivalents of TBAF, THF, 25°C , 8 hours, 73%; (e) same as d, 71%; (f) 5.0 equivalents of 2,4,6-trichlorobenzoylchloride, 6.0 equivalents of Et_3N , THF, 25°C , 15 minutes, then add to a solution of 10.0 equivalents of 4-DMAP in toluene (0.002 M based on 73), 25°C , 12 hours, 77%; (g) same as f, 76%; (h) 20% CF_3COOH (by volume) in Methylene chloride, 0°C , 1 hour, 91%; (i) see Figure 16.

Figure 19 illustrates the second stereoselective synthesis of epothilone B (2). Reagents and conditions: (a) 1.2 equivalents of LDA, THF, 0°C , 15 minutes; then 1.2 equivalents of 136 in THF, $-78 - -40^\circ\text{C}$, 1 hour; then 1.0 equivalent of 75 in THF at -78°C , 85% of 137 and 6*S*,7*R*-diastereoisomer 138 (ca 3 : 1

ratio); (b) 1.2 equivalents of TBSOTf, 2.0 equivalents of 2,6-lutidine, Methylene chloride, 0°C, 2 hours, 96%; (c) 1.0 equivalent of CSA portionwise over 1 hour, Methylene chloride:MeOH (1 : 1), 0 - 25°C, 0.5 hour, 85%; (c) 2.0 equivalents of (COCl)₂, 4.0 equivalents of DMSO, 6.0 equivalents of Et₃N, Methylene chloride, -78 - 0°C, 1.5 hours, 95%; (d) 3.0 equivalents of NaClO₂, 4.0 equivalents of 2-methyl-2-butene, 1.5 equivalents of NaH₂PO₄, tBuOH:H₂O (5:1), 25 °C, 2 hours, 90%.

Figure 20 illustrates the retrosynthetic analysis of epothilone A (1) by a solid phase olefin metathesis strategy wherein TBS = t-BuMe₂Si; filled circle = polystyrene.

Figure 21 illustrates the solid phase synthesis of epothilone a wherein: (a) 1,4-butanediol (5.0 eq.), NaH (5.0 eq.), n-Bu₄NI (0.1 eq.), DMF, 25°C, 12 hours; (b) Ph₃P (4.0 eq.), I₂ (4.0 eq.), imidazole (4.0 eq.), Methylene chloride, 25°C, 3 hours; (c) Ph₃P (10 eq.), 90°C, 12 hours (>90 % for 3 steps based on mass gain of polymer); (d) NaHMDS (3.0 eq.), THF:DMSO (1:1), 25°C, 12 hours; (e) 149 (2.0 eq.), THF, 0°C, 3 hours (>70% based on aldehyde recovered from ozonolysis); (f) 10% HF·pyridine in THF, 25°C, 12 hours; (g) (COCl)₂ (4.0 eq.), DMSO (8.0 eq.), Et₃N (12.5 eq.), -78 - 25°C (ca. 95% for 2 steps)*; (h) 144 (2.0 eq.), LDA (2.2 eq), THF, -78 - -40°C, 1 hour; then add resulting enolate to the resin suspended in a ZnCl₂ (2.0 eq.) solution in THF, -78 --40 oC, 2.0 hours (ca. 90%)*; (i) 143 (5.0 eq.), DCC (5.0 eq), 4-DMAP (5.0 eq.), 25°C, 15h (80% yield as determined by recovered heterocycle fragments obtained by treatment with NaOMe); (j) 153 (0.75 eq.), Me e

chloride, 25°C, 48 hours (52%; 154:155:156:141 = ca. 3:3:1:3); (k) 20% TFA in Methylene chloride (v/v), 92% for 157 and 90% for 158; (l) 160 [methyl(trifluoromethyl)dioxirane], MeCN, 0°C, 2 hours (70 % for 1, 45 % for 159; in addition to these products, the corresponding α -epoxides were also obtained). NaHMDS = sodium bis(trimethylsilyl)amide; DMSO = dimethyl sulfoxide; LDA = lithium diisopropylamide; TBS = t-BuMe₂Si; 4-DMAP = 4-dimethylaminopyridine. * Estimated yield. The reaction was monitored by infrared (IR) analysis of polymer-bound material and by TLC analysis of the products obtained by ozonolysis.

Figure 22 illustrates activity of epothilones on tubulin assembly. Reaction mixtures contained purified tubulin at 1.0 mg/ml, 0.4 M monosodium glutamate, 5% dimethyl sulfoxide, and varying drug concentrations. Each compound was evaluated in three different experiments and average values are shown. Samples were incubated, centrifuged, and processed at room temperature (dark circle = 71, EC₅₀ = 3.3 \pm 0.2 μ M; dark triangle = 2, EC₅₀ = 4.0 \pm 0.1 μ M; open circle = 1, EC₅₀ = 14 \pm 0.4 μ M; open square = taxol, EC₅₀ = 15. \pm 2 μ M; open triangle = 125, EC₅₀ = 22 \pm 0.9 μ M; dark square = 158, EC₅₀ = 25 \pm 1 μ M; open upside down triangle = 123, EC₅₀ = 39 \pm 2 μ M. The EC₅₀ is defined as the drug concentration that causes 50% of the tubulin to assemble into polymer. In the absence of drug, less than 5% of the tubulin was removed by centrifugation, while with high concentrations of the most active drugs, over 95% of the protein formed polymer. This suggests that at least 90% of the tubulin had the potential to interact with epothilones and taxoids. Although the EC₅₀ value obtained for Taxol was higher than that

obtained in an alternate assay as described in Hofle et al. *Angew. Chem. Int. Ed. Engl* 35, 1567-1569 (1996), the agent's role in these experiments was only as a control.

Figure 23 provides a table of results from cytotoxicity experiments with 1A9, 1A9PTX10 (β -tubulin mutant), 1A9PTX22 (β -tubulin mutant) and A2780AD cell lines showing relative activities of epothilones A (1) and B (2) as compared with synthetic analogues 71, 158, 123 and 125 as inducers of tubulin assembly and inhibitors of human ovarian carcinoma cell growth. (a) See Figure 22; (b) The growth of all cells lines was evaluated by quantitation of the protein in microtiter plates. The parental cell line 1A9, a clone of the A2780 cell line, was used to select two Taxo'-resistant sublines (1A9PTX10 and 1A9PTX22). These sublines were selected by growth in the presence of Taxol and verapamil, a P-glycoprotein modulator. Two distinct point mutations in the β -tubulin isotype M40 gene were identified. In 1A9PTX10 amino acid residue 270 was changed from Phe (TTT) to Val (GTT), and in 1A9PTX22 residue 364 was changed from Ala (GCA) to Thr (ACA). The A2780AD line is a multidrug resistant (MDR) line expressing high levels of P-glycoprotein. Relative resistance refers to the ratio of the IC_{50} value obtained with a resistant cell line to that obtained with the parental cell line.

Figure 24 illustrates the structure and numbering of epothilone A (1) and epoxalone A (2).

Figure 25 illustrates the coupling of building blocks and

construction of precursors 164 and 165. Reagents and conditions: (a) 2.4 equivalents of LDA, -40°C , THF, 1.5 hours, then 7 in THF, -40°C , 0.5 hour; 94% (45:46 ca 5:3); (b) 1.2 equivalents of (+)- $\text{Ipc}_2\text{B(allyl)}$, Et_2O , -100°C , 0.5 hour, 91%; (c) 2.0 equivalents of 163, 1.5 equivalents of DCC, 1.5 equivalents of 4-DMAP, toluene, 25°C , 12 hours, 49% (164) plus 33% (165) for two steps. TBS = tert-butyldimethylsilyl; $\text{Ipc}_2\text{B(allyl)}$ = diisopinocampheylallyl borane; LDA = lithium diisopropylamide; DCC = dicyclohexylcarbodiimide; 4-DMAP = 4-dimethylaminopyridine.

Figure 26 illustrates the olefin metathesis of precursor 164 and synthesis of epoxalones 161, 171, 170 and 172. Reagents and conditions: (a) 20 mol % of $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$, cat., CH_2Cl_2 , 25°C , 20 hours, 40% (166) plus 29% (167); (b) 20% TFA in CH_2Cl_2 , 25°C , 2 hours, 89% (168), 95% (169); (c) $\text{CH}_3\text{CN}/\text{Na}_2\text{EDTA}$ (2:1), 10.0 equivalents of CF_3COCH_3 , 8.0 equivalents of NaHCO_3 , 3.0 equivalents of Oxone $^{\circ}$, 0°C , 34% (161) plus 15% (170), 25% (171) plus 20% (172). TFA = trifluoroacetic acid. The tentative stereochemical assignments of epoxides 161, 171, 168, 169, 170 and 172 were based on the higher potencies at 161 and 171 in the tubulin polymerization assay as compared to those of 170 and 172 respectively (see Figure 28).

Figure 27 illustrates the olefin metathesis of C6-7 diastereomeric precursor 165 and synthesis of epoxalones 175-180. Reagents and conditions. (a) 20 mol % of $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$, cat., CH_2Cl_2 , 25°C , 20 hours, 25% (173) plus 63% (174); (b) 20% TFA in CH_2Cl_2 , 25°C , 2 hours, 75% (175), 72% (176); (c) $\text{CH}_3\text{CN}/\text{Na}_2\text{EDTA}$ (2:1), 10.0 equivalents of CF_3COCH_3 , 8.0

equivalents of NaHCO_3 , 3.0 equivalents of Oxone®, 0°C, 38% (177) plus 17% (178), 22% (179) plus 13% (180).

Figure 28 illustrates the effect of epoxalones, epothilones and Taxol on tubulin polymerization. The Filtration-Colorimetric Assay was used for epothilones A and B except for the 30°C incubation temperature (instead of 37°C) and the pure tubulin (instead of microtubule protein). After initial screening of all epoxalones (161, 168, 169, 170, 171, 172, 175, 176, 177, 178, 179, and 180) at 20 mM concentrations, the most potent ones (161, 168, 169, 171 and 172) were tested together with epothilones A (1) and B and Taxol at 0.1, 1.0, 2.0, 3.0, 4.0 and 5.0 mM. B = epothilone B; T = Taxol.

Figure 29 illustrates the synthesis of epothilone analogs 192, 193, 194 and 195.

Figure 30 illustrates the synthesis of epothilone analogs 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, and 210.

Figure 31 illustrates the synthesis of phosphonium analog 220.

Figure 32 illustrates the synthesis of epothilone advanced intermediate macrolides 229 and 230.

Figure 33 illustrates the synthesis of epothilone analogs 233, 234, 235, and 236.

Figure 34 illustrates the synthesis of advanced intermediate nitrile 244.

Figure 35 illustrates the synthesis of epothilone analog 249.

Figure 36 illustrates the synthesis of epothilone analog 229.

Figure 37 illustrates the synthesis of advanced intermediate aldehyde 257.

Figure 38 illustrates the synthesis of epothilone analog 263.

Figure 39 illustrates the synthesis of epothilone analog 266.

Detailed Description of the Invention

The invention is directed to epothilone analogs and methods for producing such analogs using solid and solution phase chemistries based on approaches used to synthesize epothilones A and B (Nicolaou et al. Angew. Chem. Int. Ed. Engl. 35, 2399-2401 (1996); Nicolaou et al. Angew. Chem. Int. Ed. Engl. 36, 166-168 (1997); Nicolaou et al. Angew. Chem. Int. Ed. Engl., 36, 525-527 (1997)).

The following examples illustrate methods for the total synthesis of epothilone A (1), epothilone B (2), designed analogs and the generation of epothilone libraries. The examples rely on the olefin metathesis reaction and macrocyclization as a means to form the macrocyclic ring. The disclosed methods promise the discovery of anticancer agents which will be superior to existing ones. The examples represent exemplary conditions which demonstrate the versatility of the methodology and are not meant to be restrictive with the models disclosed.

Example 1. Solution phase synthesis of epothilone A and B and analogs using an olefin metathesis approach (Figures 1-10)

A method using the olefin metathesis approach to synthesize epothilone A (1) and several analogs (39-41, 42-44, 51-57, 58-60, 64-65, and 67-69) is described (Figures 1-10). In this example, we describe the details of our olefin metathesis approach to epothilone A (1) and its application to the synthesis of several of its analogs. Key building blocks 6, 7 and 8 were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor 4 via an aldol reaction and an esterification coupling. Olefin metathesis of compound 4, under the catalytic influence of $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ catalyst, furnished *cis*- and *trans*-cyclic olefins 3 and 48. Epoxidation of 49 gave epothilone A (1) and several analogs, whereas epoxidation of 50 resulted in additional epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

A. Retrosynthetic Analysis and Strategy (Figure 2)

The structure of epothilone A (1) is characterized by a 16-membered macrocyclic lactone carrying a cis-epoxide moiety, two hydroxyl groups, two secondary methyl groups, and a gem dimethyl group, as well as a side-chain consisting of a trisubstituted double bond and a thiazole moiety (Figure 1). With its seven stereocenters and two geometrical elements, epothilone A (1) presents a considerable challenge as a synthetic target, particularly with regard to stereochemistry and functional group sensitivity. In search for a suitable synthetic strategy, we sought to apply new principles of organic synthesis and, at the same time, retain optimum flexibility for structural diversity and construction of libraries.

In recent years, the olefin metathesis reaction became a powerful tool for organic synthesis (For the development of the olefin metathesis as a ring forming reaction, see: Zuercher et al. J. Am. Chem. Soc. 1996, 118, 6634-6640; Schwab et al. J. Am. Chem. Soc. 1996, 118, 100-110; Grubbs et al. Acc. Chem. Res. 1995, 28, 446-452; Tsuji et al. Tetrahedron Lett. 1980, 21, 2955-2959; Katz et al. Tetrahedron Lett. 1976, 4247-4250; Katz et al. Tetrahedron Lett. 1976, 4241-4254; Katz et al. J. Am. Chem. Soc. 1976, 98, 606-608; Katz et al. Advances in Organomet. Chem. 1977, 16, 283-317).

In particular, a number of publications report application of this chemistry to the construction of macrocycles (For a number of applications of the olefin metathesis reaction in medium and large ring synthesis, see: Borer et al. Tetrahedron Lett. 1994, 35, 3191-3194; Clark et al. J. Am. Chem. Soc. 1995,

117, 12364-12365; Houri et al. J. Am. Chem. Soc. 1995, 117, 2943-2944; Fürstner et al. J. Org. Chem. 1996, 61, 3942-3943; Martin et al. Tetrahedron 1996, 52, 7251-7264; Xu et al. J. Am. Chem. Soc. 1996, 118, 10926-10927).

Inspection of the structure of epothilone A (1; Figure 2) reveals the intriguing possibility of applying the olefin metathesis reaction to bis(terminal) olefin 4 to yield the cis-olefin containing macrocyclic lactone 3, which could be converted to the natural product by simple epoxidation, as retrosynthetically outlined in Figure 2. Daring as it was, this strategy has the potential of delivering both the cis- and trans-cyclic olefins corresponding to 4 for structural variation. Proceeding with the retrosynthetic analysis, an esterification reaction was identified as a means to allow disconnection of 4 to its components, carboxylic acid 5 and secondary alcohol 6. The aldol moiety in 5 allows the indicated disconnection, defining the aldehyde 7 and keto acid 8 as potential intermediates. Carboxylic acid 8 can then be traced to intermediate 9, whose asymmetric synthesis via allylboration of the known keto aldehyde 12 is straightforward. An asymmetric allylboration can also be envisioned as a means to construct alcohol 6, leading to precursor 10, which can be derived from the known thiazole derivative 11. This retrosynthetic analysis led to a highly convergent and flexible synthetic strategy, the execution of which proved to be highly rewarding in terms of delivering epothilone A (1) and a series of analogs of this naturally occurring substance for biological screening (Figure 2).

B. Construction of Key Building Blocks and Models as illustrated in Figures 3 - 6

As a prelude to the total synthesis, a number of building blocks were synthesized and utilized in model studies. Thus, fragments 7, 18a, 18b and 21 (Figure 3; schemes A-C) were targeted for synthesis. Aldehyde 7 was constructed by two different routes, one of which is summarized in Figure 3A. Thus, Oppolzer's acylated sultam derivative 13 (Oppolzer et al. Tetrahedron Lett. 1989, 30, 5603-1989; Oppolzer et al. Pure & Appl. Chem. 1990, 62, 1241-1250) was alkylated with 5-iodo-1-pentene in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) to furnish compound 14 as a single diastereoisomer (by ^1H NMR). Lithium aluminum hydride reduction of 14 gave alcohol 15 in 60% overall yield from sultam 13. Oxidation of 15 with tetrapropylammonium perruthenate(VII) (TPAP) and 4-methylmorpholine-N-oxide (NMO) yielded the desired aldehyde 7 in 95% yield.

The synthesis of the two antipodal alcohols 18a and 18b is outlined in Figure 3B. Thus, glycidols 16a and 16b were converted to the corresponding tert-butyldiphenylsilyl ethers (OTPS) 17a (90% yield) and 17b (94% yield), respectively, by a standard procedure (TPSCl, imidazole), and then to 18a (86% yield) and 18b (83% yield) by reaction with the vinyl cuprate reagent derived from copper(I) cyanide and vinyl lithium.

Figure 3C summarizes the synthesis of the third required building block, keto acid 21, starting with the known and readily available keto aldehyde 12 (Inuka et al. J. Org. Chem. 1967, 32,

404-407). Condensation of 12 with the sodium salt of phosphonate 19 produced α,β -unsaturated ester 20 in 99% yield. Cleavage of the tert-butyl ester with CF_3COOH in Methylene chloride resulted in a 99% yield of carboxylic acid 21.

With the requisite fragments in hand, we turned our attention to a feasibility study of the olefin metathesis strategy. Figure 4 summarizes the results of our work in this area. Thus, coupling of fragments 18a and 21, mediated by the action of EDC and 4-DMAP, led to ester 22a in 86% yield. Aldol condensation of the lithium enolate of keto ester 22a (generated by the action of LDA) and aldehyde 7 resulted in the formation of aldols 23 and 24 in ca. 4:3 ratio. Chromatographic separation allowed the isolation of pure 23 (42% yield) and 24 (33% yield). The stereochemical assignments of compounds 23 and 24 were based on an X-ray crystallographic analysis of a subsequent intermediate as will be described below. In Figure 4, exposure of 23 to the $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ catalyst in Methylene chloride solution under high-dilution conditions at 25°C for 12 hours resulted in clean formation of a single trans-macrocyclic olefin (25) ($J_{12,13} = 15.5 \text{ Hz}$) in 85% yield. Similar treatment of 24 generated the diastereomeric trans-olefin 26 ($J_{12,13} = 15.2 \text{ Hz}$) as the sole product in 79% yield. Desilylation of 25 and 26 with TBAF and AcOH in THF at 25°C gave dihydroxy lactones 27 (92% yield) and 28 (95% yield, mp 128-129°C, EtOAc-hexanes), respectively.

X-ray crystallographic analysis of macrocyclic diol 28 revealed the trans nature of the double bond and defined the

stereochemistry of all stereogenic centers. Comparison of the ^1H NMR spectra of 26 and 28 with those of 25 ($J_{12,13} = 15.5$ Hz), 27, 31 ($J_{12,13} = 15.7$ Hz) and 32 (vide infra) supported the trans geometry of the double bond generated by the olefin metathesis, and the C6-C7 stereochemistry. Therefore, the original assignment (Nicolaou et al. *Angew. Chem. Int. Ed. Engl.* 1996, 35, 2399-2401) of the cis geometry for this double bond and the C6-C7 stereochemistry of the aldol products in these model systems should now be revised as shown. Ironically, it was this erroneous, but encouraging assignment that let us to embark on the final plan to synthesize epothilone A by the olefin metathesis approach. As events unfolded (vide infra), the real system produced both the cis- and the trans-cyclic olefins and the metathesis approach turned out to be fruitful.

For the purposes of analog synthesis, the 15R fragment 18b was utilized in these studies as well, as shown in Figure 5. Coupling of 18b and 21 with DCC and 4-DMAP led to a 95% yield of ester 22b, the enantiomer of 22a. LDA-mediated aldol condensation of 22b with aldehyde 7 furnished aldols 29 (54% yield) and 30 (24% yield), which are diastereomeric with 23 and 24 of Figure 4. Olefin metathesis of 29 and 30 with the $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ catalyst led to cyclic systems 31 ($J_{12,13} = 15.7$ Hz) (80% yield) and 32 ($J_{12,13} = 15.4$ Hz) (81% yield), respectively. Compounds 27, 28, 31 and 32 may serve as suitable precursors for the construction of a series of designed epothilones for biological investigations. At this juncture, however, it was considered more urgent to investigate the compatibility of the zole side-chain with the conditions of

olefin metathesis and epoxidation.

To this end, the chemistry shown in Figure 6 was studied. The enolate of keto acid 21 (2.3 equivalents of LDA, THF, -78°C) reacted with aldehyde 7 to afford hydroxy acids 33 and 34 as a mixture of C6-C7 (ca 2:3 by ^1H NMR) in good yield. This mixture was coupled with alcohol 6 in the presence of EDC and 4-DMAP, to afford two diastereomeric esters, 35 and 36 (29% and 44% yield, respectively, for two steps). Both products, 35 and 36 were subjected to the olefin metathesis reaction, and we were delighted to observe a smooth ring closure leading to trans-macrocycles 37 ($J_{12,13} = 15.5$ Hz) (86%) and 38 ($J_{12,13} = 15.0$ Hz) (66%). With cyclized product 37 and 38 in hand, we then proceeded to demonstrate the feasibility of epoxidizing the C12-C13 double bond in the presence of the sulfur and olefin functionalities in the thiazole side chain. Thus, treatment of both 37 and 38 with 0.9-1.2 equivalents of mCPBA in CHCl_3 at 0°C resulted in the formation of epoxides 39 (or 40) (40%), 40 (or 39) (25%, stereochemistry unassigned), and 41 (18%, stereochemistry unassigned), as well as 42 (or 43) (22%), 43 (or 42) (11%) and 44 (7%) along with some unidentified side products. These results paved the way for the final drive towards epothilone A (1). More recently we found that methyl(trifluoromethyl)dioxirane (Yang et al. J. Org. Chem. 1995, 60, 3887-3889) gives superior results in the epoxidation reactions in regard to regioselectivity and yields. Thus, olefins 37 and 38 were converted to epoxides 39 (or 40) (45%) and 40 (or 39) (28%), and epoxides 42 (or 43) (60%) and 43 (or 42) (15%), respectively. No side-chain epoxidation was observed in

either case.

C. Total Synthesis of Epothilone A and Analogs

Encouraged by the results of the model studies described above, we proceeded to assemble epothilone A (1). Figure 7 shows the initial stages of the construction beyond the key building blocks 6-8. Thus, aldol condensation of 8 (2.3 equivalents of LDA) with aldehyde 7 afforded diastereomeric products 45 and 46 (ca 3:2 ratio by ^1H NMR), which were coupled as a mixture with allylic alcohol 6 in the presence of EDC and 4-DMAP, to afford, after chromatographic purification, pure esters 4 (52% overall from 8) and 43 (31% overall from 8).

The olefin metathesis reaction of 4 (6R,7S stereochemistry as proven by conversion to epothilone A) proceeded smoothly in the presence of the $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ catalyst, as shown in Figure 8, to afford cyclic systems 8 ($J_{12,13} = 10.5$ Hz) (46%) and 48 ($J_{12,13} = 15.0$ Hz) (39%). The silyl ethers from 3 and 48 were removed by exposure to CF_3COOH in Methylene chloride, affording dihydroxy compounds 49 (90% yield) and 50 (92% yield), respectively.

The cis-olefin 49 was converted to epothilone A (1) by the action of mCPBA (0.8-1.2 equivalents) in a reaction that, in addition to 1 (35% yield), produced the isomeric epoxides 51 (13% yield), 52 (or 53) (9% yield, stereochemistry unassigned) and 53 (or 52) (7% yield, stereochemistry unassigned), as well as bis(epoxides) 54 (or 55) and 55 (or 54) (10% total yield, stereochemistry unassigned). Reaction of olefin 49 with excess

mCPBA (1.3-2.0 equivalents) gave a different product distribution: 1 (15%), 51 (10%), 52 (or 53) (10%), 53 (or 52) (8%), 54 (or 55) (8%), 55 (or 54) (7%), 56 (5%), and 57 (5%). The action of dimethyldioxirane (Murray et al. J. Org. Chem. 1985, 50, 2847-2853) (Methylene chloride, 0°C) on 49 gave mainly 1 (50%) and 51 (15%), together with small amounts of 53 (or 54) and 54 (or 53) (10% total yield).

However, we found that the preferred procedure for this epoxidation was the one employing methyl(trifluoromethyl)dioxirane (CH_3CN , Na_2EDTA , NaHCO_3 , Oxone®, 0°C; Yang et al. J. Org. Chem. 1995, 60, 3887-3889), a method that furnished epothilone A (1) in 62% yield, together with smaller amount of its α -epoxide epimer 51 (13% yield). Chromatographically purified synthetic epothilone A (1) exhibited identical properties to those of an authentic sample (TLC, HPLC, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, and Mass spec). Further, epoxidation of pure 1 with mCPBA (0.8-1.1 equivalents) resulted in the formation of bis(epoxides) 54 (or 55) (35%) and 55 (or 54) (32%) along with sulfoxide 57 (6%), confirming the C12-C13 stereochemical assignments shown in Figure 8. Under similar conditions, α -isomeric epoxide 51 was recovered unreacted.

The trans-olefinic compound 50 gave rise to another series of epothilones A (58-60) as shown in Figure 9. Thus, epoxidation of 50 with 1.0 equivalent of mCPBA furnished compounds 58 (or 59) (5%, stereochemistry unassigned), 59 (or 58) (5%, stereochemistry unassigned) and 60 (60%, stereochemistry unassigned). Similarly, epoxidation of 50 with 1.0 equivalent of dimethyldioxirane

resulted in the formation of 58 (or 59) (10%), 59 (or 58) (10%) and 60 (40%). Interestingly, however, the action of methyl(trifluoro-methyl)dioxirane led only to 58 (or 59) (45%) and 59 (or 58) (35%) in a much cleaner fashion.

In order to expand the epothilone A library, we utilized the 6S,7R-stereoisomer 61 (obtained from 47 by CF₃COOH-induced desilylation in 90% yield) in the olefin metathesis reaction, to afford cyclic compounds 62 ($J_{12,13} = 9.8$ Hz) (20%) and 63 ($J_{12,13} = 15.0$ Hz) (69%) (Figure 10). Epoxidation of the dihydroxy macrocyclic compound 62 with mCPBA (0.8-1.2 equivalents) in CHCl₃ at -20 to 0°C gave isomeric epoxides 64 (or 65) (25%) and 65 (or 64) (23%). Side-chain epoxide 66 was not isolated in this case. Similarly, diol 63 furnished 67 (or 68) (24%), 68 (or 67) (19%), and 69 (31%) under the same reaction conditions. The stereochemistry of epothilones 64-69 remains unassigned. Again, epoxidation of compounds 62 and 63 using methyl(trifluoromethyl)dioxirane resulted in epoxides 64 (or 65) (58%) and 65 (or 64) (29%), and in epoxides 67 (or 68) (44%) and 68 (or 67) (21%), respectively, in a cleaner fashion (Figure 10).

In example 1, we illustrate methods culminating in the total synthesis of epothilone A (1) and of analogs by an olefin metathesis approach. Furthermore, besides defining the scope and limitations of this new methodology in total synthesis, the methods provide a series of epothilone A analogs for biological investigations and further chemical explorations. The high convergence and relative simplicity of the chemistry involved in this construction make this strategy amenable to combinatorial

synthesis for the generation of large libraries of these structures, as illustrated in a later example.

Example 2. Solution phase synthesis of epothilone A and B and analogs using a macrolactonization approach as illustrated in Figures 11-19.

In this example, we illustrate methods for the total synthesis of both epothilones A (1) and B (2) and of a number of analogs using our macrolactonization strategy (Nicolaou Angew. Chem. Int. Ed. Engl. 1997, 36, 525-527). The reported strategy relies on a macrolactonization approach and features selective epoxidation of the macrocycle double bond in precursors 70 and 71 (Figure 1), respectively, as well as high convergency and flexibility. Building blocks 76-79 and 82 were constructed by asymmetric processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogs by a relatively short route. The utilization of intermediate 81, obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone 80 (Figure 17), in combination with a stereoselective aldol reaction with the modified substrate 136 (Figure 19) improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

A. Retrosynthetic Analysis

Figure 11 outlines the macrolactonization-based retrosynthetic analysis of epothilones A (1) and B (2). Thus, retrosynthetic removal of epoxide oxygen from 1 and 2 reveals

the corresponding 2-olefins, 70 and 71, as potential precursors, respectively. The second major retrosynthetic step along this route is the disconnection of the macrocyclic ring at the lactone site, leading to hydroxy acids 72 and 73 as possible key intermediates. Moving further along the retrosynthetic path, an aldol-type disconnection allows the generation of keto acid 76 as a common intermediate, and aldehydes 74 and 75 as reasonable building blocks for 72 and 73, respectively. Keto acid 76 can be envisioned to arise from an asymmetric allylboration of the corresponding aldehyde, followed by appropriate elaboration of the terminal olefin. The larger intermediates, 74 and 75, can be disconnected by two slightly different ways. The first disconnection (route a) involves a retro-Wittig type reaction accompanied by a number of functional group interchanges, leading to compounds 77, 78 and 79. The second disconnection, specifically sought for its potential to address the geometry issue of the trisubstituted double bond of epothilone B (2) (route b), involves: (i) a retro-Enders alkylation, leading to hydrazone 80 and iodide 81; and (ii) a retro-Wittig type disconnection of the latter intermediate (81) to reveal aldehyde 82 and stabilized ylide 83 as potential building segments. An asymmetric allylboration of 82 then points to Brown's chiral allylborane, and an aldehyde carrying the required thiazole moiety as potential starting points.

B. Total Synthesis

1. Construction of Building Blocks (Figures 12-13):

The strategy derived from the retrosynthetic analysis discussed above (Figure 1), required building blocks 76-79, 82,

and related compounds. Their construction in optically active form proceeded as follows. Figure 12 summarizes the synthesis of keto acid 76 starting with the known keto aldehyde 84. Thus, addition of (+)- $\text{Ipc}_2\text{B(allyl)}$ to 84 in ether at -100°C resulted in the formation of enantiomerically enriched alcohol 85 (74% yield, ee >98% by Mosher ester determination). Silylation of 85 with tert-butyldimethylsilyl triflate (TBSOTf) furnished, in 98% yield, silyl ether 86. The conversion of terminal olefin 86 to carboxylic acid 76 was carried out in two steps: (i) ozonolysis in Methylene chloride at -78°C followed by exposure to Ph_3P to give aldehyde 87 (90% yield); and (ii) oxidation of 87 with NaClO_2 in the presence of 2-methyl-2-butene and NaH_2PO_4 in $\text{tBuOH-H}_2\text{O}$ (5:1) (93% yield).

The synthesis of the thiazole-containing fragments 82 and 79 was accomplished as shown in Figure 12. Thus, the known thiazole derivative 88 was reduced with DIBAL (1.6 equivalents, Methylene chloride, -78°C) to aldehyde 89 (90% yield), which reacted with the appropriate stabilized ylide [$\text{Ph}_3\text{P}=\text{C(Me)CHO}$] in benzene at 80°C to afford the required (E)- α,β -unsaturated-aldehyde 90 in 98% yield. Addition of (+)- $\text{Ipc}_2\text{B(allyl)}$ to 90 in ether/pentane at -100°C gave allylic alcohol 91 in 96% yield (>97% ee by Mosher ester analysis). Protection of the hydroxyl group in 91 as a TBS ether (TBSCl, imid., DMF, 99% yield), followed by chemoselective dihydroxylation (OsO_4 , cat., NMO) of the terminal olefin (95% yield) and Pb(OAc)_2 cleavage of the resulting diol (98% yield), furnished aldehyde 82 via intermediate 92. Finally, NaBH_4 reduction of 82 (96% yield), followed by iodination (I_2 , imidazole, Ph_3P , 89% yield) and phosphonium salt formation (Ph_3P ,

neat, Δ , 98% yield) gave the requisite fragment 79 via the intermediacy of alcohol 93 and iodide 94.

The construction of aldehyde 77 and ketone 78 proceeded from SAMP hydrazone 80 as shown in Figure 13. Thus, reaction of propionaldehyde with SAMP, furnished 80, which upon sequential treatment with LDA (THF, 0°C) and 4-iodo-1-benzyloxybutane (THF, -100 to 0°C) led to compound 95 in 92% yield and >98% de (¹H NMR). Cleavage of the hydrazone moiety by exposure to ozone (Methylene chloride, -78°C, 77% yield), or by treatment with MeI at 60°C followed by acidic workup (aq HCl, 86% yield), followed by NaBH₄ reduction of the resulting aldehyde (96), furnished alcohol 97 in 98% yield. The latter compound (97) was then silylated with TBSCl in Methylene chloride in the presence of Et₃N and 4-DMAP to afford silyl ether 98 in 95% yield. Cleavage of the benzyl ether in 98 by hydrogenolysis [H₂, Pd(OH)₂, cat., THF, 50 psi], gave primary alcohol 99 (95% yield), which was smoothly oxidized to the desired aldehyde 77 under Swern conditions [(COCl)₂, DMSO, Et₃N, 98% yield]. Addition of MgMgBr to 77 proceeded in 84% yield, and was followed by TPAP-NMO oxidation of the resulting secondary alcohol (100) to give the other required building block, ketone 78, in 96% yield (Figure 13).

With the appropriate building blocks at hand the convergent approach to epothilones A (1) and B (2) could now enter its second phase.

2. Total Synthesis of Epothilones A as illustrated in

Figure 14

The couplings of building blocks 76, 77 and 79 and the total synthesis of epothilone A (1) and its 6S,7R-diastereoisomers (111 and 112) are shown in Figure 14. Thus, generation of the ylide from phosphonium salt 79 with sodium bis(trimethylsilyl)amide (NaHMDS), followed by reaction with aldehyde 77 resulted in the formation of the desired Z-olefin 101 ($J_{12,13} = 10.8$ Hz, obtained from decoupling experiments) as the predominant product in 77% yield, [Z:E ca 9:1; the minor isomer (E) was removed chromatographically in subsequent steps]. Parenthetically, key intermediate 101 was also prepared by Wittig coupling of phosphonium salt 114 and aldehyde 82 in a reversal of the reacting functionalities of the two fragments as shown in Figure 15. Thus, alcohol 99 was directly converted to iodide 113 by the action of I_2 , imidazole, and Ph_3P (91% yield), and then to phosphonium salt 114 by heating with Ph_3P (91% yield). Generation of the ylide from 114 with equimolar amounts of NaHMDS in THF, followed by reaction with aldehyde 82 yielded Z-olefin 101 in 69% and in ca 9:1 ratio with its E-isomer.

Returning to Figure 14, selective desilylation of the primary hydroxyl group from 101, was achieved by the action of camphorsulfonic acid (CSA) in MeOH:Methylene chloride (1:1), leading to hydroxy compound 102 in 86% yield. Oxidation of 102 to aldehyde 74 was then carried out using $SO_2 \cdot pyr.$, DMSO and Et_3N (94% yield). With the availability of 74, we were then in a position to investigate its aldol condensation with keto acid 76. It was found that the optimum conditions for this coupling reaction required generation of the dilithio derivative of 76 (1.2

equivalents) with 3.0 equivalents of lithium diisopropylamide (LDA) in THF (-78 to -40°C), followed by addition of aldehyde 74 (1.0 equivalent), resulting in the formation of a mixture of the desired product 103a and its 6S,7R-diastereoisomer 103b in ca 1:1 ratio and in high yield. Despite the lack of stereoselectivity in this reaction, the result was welcome at least with regard to the prospect it provided for the construction of the 6S,7R-diastereoisomer of epothilones A and B. This mixture was then carried through to the stage of carboxylic acids 105 and 106 (Figure 14), where it was chromatographically separated to its components. Thus, exposure of 103a/103b to excess of TBSOTf and 2,6-lutidine furnished a mixture of tetra-silylated products 104a/104b, which was then briefly treated with K₂CO₃ in MeOH, to afford, after silica gel flash or preparative layer chromatography, carboxylic acids 105 (31% overall yield from 7) and 106 (30% overall yield from 74) (105: R_f = 0.61; 39: R_f = 0.70, silica gel, 5% MeOH in Methylene chloride). The indicated stereochemistry at C7 and C6 in compounds 105 and 106 was assigned later and was based on the successful conversion of 105 to epothilone A (1) as described below.

At this stage, it was necessary to selectively remove the TBS group from the allylic hydroxyl group of 105, so as to allow macrolactonization of the seco-acid substrate (72). This goal was achieved by treatment of 38 with tetra-n-butylammonium fluoride (TBAF) in THF at 25°C, generating the desired hydroxy acid 72 in 78% yield. The key macrolactonization reaction of 72 was carried out using the Yamaguchi method (2,4,6-trichlorobenzoyl chloride, Et₃N, 4-DMAP) at 25°C, affording

compound 108 in 90% yield. Removal of both TBS groups from 108 (CF_3COOH , Methylene chloride, 0°C) furnished diol 70 in 92% yield. Finally, treatment of 70 with methyl(trifluoromethyl)dioxirane led cleanly to epothilone A (1) (62% yield) and its α -epoxide epimer (13% yield). Synthetic epothilone A (1) was chromatographically purified (preparative thin layer chromatography, silica gel) and exhibited identical properties to those of an authentic sample (TLC, HPLC, $[\alpha]_D$, IR, ^1H and ^{13}C NMR and HRMS).

A similar sequence was followed for the synthesis of the 6S,7R-diastereoisomers 111 and 112 of epothilone A (1) from compound 106 (Figure 14) via intermediates 107 (82% yield from 106), 109 (85% yield from 107), and 110 (95% yield from 109). Epothilone 111 was obtained as the major product, together with its α -epoxide epimer 112 (87% total yield, ca 2:1 ratio) from olefinic precursor 110 by methyl(trifluoromethyl)dioxirane epoxidation.

3. Total Synthesis of Epothilones B (Figure 16)

The first approach to epothilone B (2) was designed with the aim of delivering, not only the natural substance, but also its 12S-diastereoisomer 125 (Figure 16), which in turn required the generation of both 12Z- and 12E-olefins. To this end, the ylide generated from phosphonium salt 79 with equimolar amounts of NaHMDS in THF, was reacted with ketone 78 to afford a mixture of Z- and E-olefins 115 (ca 1:1 ratio) in 73% total yield. This mixture was carried through the sequence to the stage of carboxylic acids 119 and 120 (see Figure 16 for details) which

were chromatographically separable. Carboxylic acid 120 (mixture of geometrical isomers) with the wrong stereochemistry at C6 and C7 (6S,7R) was abandoned at this stage, whereas the mixture of Z- and E-isomers 119 with the correct stereochemistry at C6 and C7 (6R,7S) was taken to the macrolactone stage (compounds 121 and 122) via hydroxy acid 6', by: (i) selective desilylation of the C15 hydroxyl group (TBAF, THF, 75% yield); and (ii) Yamaguchi cyclization (37% yield of 121, plus 40% of 122). Deprotection of bis(silylether) 121 by treatment with CF₃COOH in Methylene chloride afforded diol 71 in 91% yield. Finally, epoxidation of 71 with mCPBA in benzene at 3°C gave epothilone B (2), together with its α-epoxide epimer 124 in 66% total yield and ca 5:1 ratio (¹H NMR) while the use of dimethyldioxirane, gave 2 and 124 in 75% total yield in the same ratio (ca 5 : 1 in favor of 2). Epoxidation of 71 with methyl(trifluoromethyl)dioxirane in CH₃CN at 0°C improved the yield of epothilone B (2) and its α-epimer 124 to 85%, but did not significantly change the diastereoselectivity of the reaction. Epothilone B (2) was purified by silica gel preparative layer chromatography and exhibited identical properties (TLC, HPLC, [α]_D, IR, ¹H and ¹³C NMR, and HRMS) with those of an authentic sample.

By the same sequence, and in similar yields, the macrocycle 122 containing the E-endocyclic double bond (Figure 16), was converted to the 12S-epimeric epothilone B 125 and its α-epoxy epimer 126 via dihydroxy macrocyclic compound 123 (epoxidation with methyl(trifluoromethyl)dioxirane).

In order to improve the efficiency of the route to

epothilone B (2), a more stereoselective total synthesis was devised and executed as follows. Figure 17 addresses the stereoselective construction of intermediate 75 with the 12Z-geometry. Thus, condensation of the stabilized ylide 83 (obtained from 4-bromo-1-butene by: (i) phosphonium salt formation; (ii) anion formation with NaHMDS; and (iii) quenching with MeOC(O)Cl) with aldehyde 82 proceeded smoothly to afford olefinic compound 127 in 95% yield and as a single isomer. Reduction of the methyl ester in 127 with DIBAL resulted in the formation of allylic alcohol 128 (98% yield), which was deoxygenated by first reacting it with $\text{Ph}_3\text{P}-\text{CCl}_2$, and thence with LiEt_3BH , to afford the desired trisubstituted 12Z-olefin 130, via chloride 129, in 82% overall yield. The latter compound 130 was regioselectively hydroborated with 9-BBN and converted to the primary alcohol 131 (91%), which was then treated with I_2 -imidazole- Ph_3P to afford iodide 81 (92% yield). This iodide was then used in an Enders alkylation reaction with SAMP hydrazone 80 to give compound 132 as a single isomer (^1H NMR) and in 70% yield. Treatment of hydrazone 132 with monoperoxyphthalic acid magnesium salt (MMPP) in MeOH:phosphate pH 7 buffer (1:1) resulted in clean conversion to nitrile 133 (80% yield), which formed aldehyde 75 (82% yield) upon exposure to DIBAL at -78°C in toluene solution.

The homogeneous aldehyde 75 was converted to epothilone B (2) by the sequence depicted in Figure 18. Thus, condensation of the dianion of 76 with 75 as before (Figure 16), produced two diastereoisomers, 117a (6R,7S stereoisomer) and 117b (6S,7R stereoisomer) in high yield, and in ca 1.3:1.0 ratio (117a:117b).

This mixture was carried through the indicated sequence to carboxylic acids 119 (32% overall yield from 75) and 119 (28% overall yield from 75), which were separated by silica gel preparative layer or flash column chromatography and taken individually further along the sequence as described for the corresponding stereoisomeric mixtures shown in Figure 16. Thus, 119 was selectively deprotected with TBAF to afford hydroxy acid 73 (73% yield), which was then cyclized to macrolactone 121 in 77% yield by the Yamaguchi method. The conversion of 121 to epothilone B (2) and its α -epoxide epimer 119 has already been described above (Figure 16).

In an effort to improve the diastereoselectivity of the aldol condensation between C1-C6 and C7-C15 fragments, the following chemistry was explored (Figure 19). Thus, ketone 136 (prepared from ketone 87, Figure 12, by selective reduction, followed by silylation) was converted to its enolate with stoichiometric amounts of LDA and reacted with aldehyde 75 (Z-isomer), affording coupling products 137 and 138 in 85% total yield and ca 3:1 ratio, with the desired compound 137 predominating as proven by its conversion to 119 and epothilone B (2). Thus, chromatographic purification (silica gel, 20% ether in hexanes) led to 137, which was efficiently transformed to the previously synthesized intermediate 119 (Figure 18) as follows. The newly generated hydroxyl group in 137 was silylated with TBSOTf-2,6-lutidine to furnish 139 (96% yield), which was then selectively desilylated at the primary position by the mild action of camphorsulfonic acid (CSA) in MeOH-Methylene chloride, leading to 140 (85%). Finally, sequential oxidation of the

primary alcohol with $(\text{COCl})_2$ -DMSO-Et₃N (95% yield) and NaClO_2 - NaH_2PO_4 (90% yield) led to hydroxy acid 119 via aldehyde 141. The conversion of 119 to 2 has already been described above (Figure 18). This sequence represents a stereoselective and highly efficient synthesis of epothilone B (2) and opens the way for the construction of further analogs within this important family of microtubule binding agents.

The chemistry described in this example defines a concise methodology for the construction of epothilones A (1) and B (2) based on a macrolactonization strategy, and which enjoys convergency and flexibility for structural diversity. The methodology is not limited to epothilones A (1) and B (2), but can be extended to numerous intermediates and structural analogs included herein. In addition, the resultant analogs will play a crucial role in elucidating structure-activity relationships of these new substances and in determining their relevance to cancer chemotherapy. Binding assays, *vide infra*, have demonstrated that compounds 70, 71, 123 and 125 show binding affinities to microtubules comparable to those of epothilones A (1), B (2), and TaxolTM.

Example 3: Solid phase synthesis of the epothilones as illustrated in Figures 20-21.

In this example, we demonstrate the first solid phase synthesis of epothilone A (1) and the total synthesis of epothilone B (2), the generation of a small epothilone library, and the identification of a synthetic epothilone that interacts

with tubulin more potently than epothilones A (1) and B (2) and Taxol (Figures 20-24). The solid phase construction of 1 may herald a new era of natural products synthesis and, together with the solution phase synthesis of 2, paves the way for the generation of large combinatorial libraries of these important molecules for biological screening.

The strategy for the solid phase synthesis of epothilone A (1) was based on the retrosynthetic analysis indicated in Figure 20 (Nicolaou et al. *Angew. Chem. Int. Ed. Engl.* 35, 2399-2401 (1996); Yang et al. *Angew. Chem. Int. Ed. Engl.* 36, 166-168 (1997)). Thus, it was anticipated that the three requisite fragments (143-145), one on a solid support (145), would be coupled together sequentially through an aldol reaction, an esterification reaction, and an olefin metathesis reaction, the latter simultaneously cyclizing and liberating the product from the solid support (144+145+143 leads to 142 which leads to 141; Figure 20). A simple desilylation and epoxidation reaction would then complete the total synthesis of epothilone A (1) and analogues thereof (141 leads to 1; Figure 20). The outlook for obtaining two products at each of the aldol, metathesis, and epoxidation steps was considered advantageous for the purposes of library generation.

As illustrated in Figure 21, Merrifield resin (146) was converted to phosphonium salt 147 in >90% yield by sequential reaction with: (i) 1,4-butanediol-NaH-n-Bu₄NI catalyst; (ii) Ph₃P-iodine-imidazole; and (iii) Ph₃P. Preferred alternative resins, other than the Merrifield resin, employable in this

procedure include PEG-polystyrene, hydroxymethyl polystyrene, formyl polystyrene, aminomethyl polystyrene and phenolic polystyrene. Ylide 148 generated from 147 by the action of NaHMDS in THF:DMSO at 25°C, reacted with aldehyde 149 at 0°C to form olefinic compound 150 in >70% yield. The geometry of the double bond in 150 was tentatively assigned as Z, but its geometry was neither rigorously determined nor did it matter for our purposes. Desilylation of 150 with HF·pyr., followed by Swern oxidation of the resulting primary alcohol furnished aldehyde 145 in high yield (>95%). The aldol condensation of the polymer-bound aldehyde 145 with the dianion derived from keto acid 144 in the presence of ZnCl₂ in THF gave a mixture of diastereoisomers (ca 90% yield, ca 1:1 ratio). Finally, introduction of the heterocyclic segment 143 onto the growing substrate was achieved by esterification, leading to the required precursor 152 in ca 80% yield. Exposure of 152 to RuCl₂(=CHPh)(PCy₃)₂ catalyst (153) in Methylene chloride at 25°C released from the resin olefinic compounds 154-156 and 141 (52% total yield, 154:155:156:141 ca 3:3:1:3 as determined by HPLC). Compounds 154-156 and 141 could be separated either by HPLC or by preparative layer silica gel chromatography, and the two with the correct C6-C7 stereochemistry (e.g. 155 and 141) were desilylated by exposure to TFA to afford epothilone precursors 157 (92%) and 158 (90%), respectively. Epoxidation of 157 and 158 with trifluoro(methyl)dioxirane then furnished epothilone A (1, 70%) and its diastereoisomer 159 (45%), respectively. The α-epoxy isomers of 1 and 159 were also obtained in these epoxidation reactions. Pure synthetic epothilone A (1) exhibited identical properties (TLC, [α]_D, ¹H and ¹³C NMR, IR and HRMS) to those of an

authentic sample (Figure 21).

The solid phase synthesis of epothilone A (1) described herein represents a new concept for the total synthesis of natural products, traces a highly efficient pathway to the naturally occurring epothilones, and opens the way for the generation of large combinatorial epothilone libraries. The biological results demonstrate that more potent microtubule binding analogues than the parent epothilones can be obtained (e.g. compound 71; biological results *vide infra*) by chemical synthesis. Furthermore, our findings point to lipophilic substituents rather than the epoxide moiety as important elements for binding activity.

Example 4. Total Synthesis of Epoxalones A and Epoxalone
Analogues

In this example, we report the total synthesis of a novel series of designed epothilones with an oxygen instead of a sulfur atom at position 20 (see Figure 24). The name epoxalones (ep for epoxide, oxa for oxazole, one for ketone; cf epothilone: ep for epoxide, thi for thiazole, one for ketone) is proposed for this new class of compounds.

The synthesis of the epoxalone A series was based on our olefin metathesis strategy toward epothilone A (1). This highly convergent and flexible sequence led to the construction of compounds 161, 168, 169, 170, 171, 172, 175, 176, 177, 178, 179, and 180 in rapid fashion starting with building blocks 7, 8 and 163 (Figure 25). Thus, asymmetric allylboration of aldehyde 162 (obtained via the procedure by Kende et al. *Tetrahedron Lett.*

1995, 36, 4741-4744) with Brown's (+)-Ipc₂B(allyl) in Et₂O-pentane at -100°C furnished compound 163 in 91% yield and >98% ee. This alcohol was esterified with the mixture of carboxylic acids 45 and 46 (ca. 5:3 ratio) obtained by aldol condensation of fragments 8 and 7 to afford compounds 164 and 165 as a ca. 5:3 mixture (82% total yield). Chromatographic separation (flash column, silica gel, 20% EtOAc in hexanes) of this mixture gave pure diastereoisomers 164 and 165.

Subjection of precursor 164 (possessing the correct C6-C7 stereochemistry) to the olefin metathesis reaction [RuCl₂(=CHPh)(PCy₃)₂, CH₂Cl₂, 25°C] resulted in the formation of cyclic olefins 166 (40% yield) and 167 (29% yield) which were chromatographically separated (flash column, silica gel, 20% EtOAc in hexanes, 1:1) (Figure 26). Exposure of 166 to 20% trifluoroacetic acid in CH₂Cl₂ at 25°C furnished diol 168 in 89% yield. Similar treatment of 167 led to 169 (95% yield). Epoxidation of 168 with methyl(trifluoromethyl)dioxirane furnished epoxides 161 (34% yield) and 170 (15% yield) which were separated by preparative layer chromatography (silica gel, 75% EtOAc in hexanes). Similar treatment of 169 led to epoxides 171 (25%) and 172 (20%) (As illustrated in Figure 26).

A parallel sequence starting with diastereoisomer 165 led to the 6S,7R series of epoxalones 175-180 as summarized in Figure 27.

The synthesized compounds (161, 168, 169, 170, 171, 172, 175, 176, 177, 178, 179, and 180) were tested for their tubulin

assembly properties using the Filtration-Colorimetric Assay (outlined *vide infra*) at 20 mM concentrations at 30°C and with pure tubulin. The most potent ones (161, 168, 169, 171 and 172) were then assayed at 0.1, 1.0, 2.0, 3.0, 4.0 and 5.0 mM concentrations under the same conditions leading to the plots shown in Figure 28. Thus, both epoxalones 161 and 171 were found to be more potent than Taxol in inducing tubulin polymerization, whereas compounds 168, 169 and 172 showed comparable or slightly less potencies than Taxol. The high potency of the trans-epoxide epoxalone 171 is perhaps the most striking observation in these studies and holds true for the corresponding trans-epoxides of epothilones A and B.

Example 6. Biological Evaluation of Synthesized Compounds

We have carried out microtubule assays following literature procedures and evaluated synthesized compounds for their ability to form and stabilize microtubules. Cytotoxicity studies have also been carried out in our laboratories and preliminary data is disclosed *vide infra*.

The synthesized epothilones were tested for their action on tubulin assembly using purified tubulin with an assay developed to amplify differences between compounds more active than Taxol. As demonstrated in Figure 22, both epothilone B (2) ($EC_{50} = 4.0 \pm 1\text{mM}$) and its progenitor 71 ($EC_{50} = 3.3 \pm 0.2\text{mM}$) were significantly more active than Taxol ($EC_{50} = 15.0 \pm 2\text{mM}$) and epothilone A (1) ($EC_{50} = 14.0 \pm 0.4\text{mM}$), whereas compounds 125, 158 and 123 were less effective than Taxol (Lin et al. Cancer

Chemother. Pharmacol. 38, 136-140 (1996); Rogan et al. Science 244, 994-996 (1984)).

As shown in Figure 23, cytotoxicity experiments with 1A9, 1A9PTX10 (β -tubulin mutant), 1A9PTX22 (β -tubulin mutant) and A2780AD cell lines revealed a number of interesting results (Figure 23). Thus, despite its high potency in the tubulin assembly assay, compound 71 did not display the potent cytotoxicity of 2 against 1A9 cells, being similar to 1 and Taxol. These data suggest that while the C12-C13 epoxide is not required for the epothilone-tubulin interaction, it may play an important role in localizing the agent to its target within the cell. Like the naturally occurring epothilones 1 and 2, analogue 71 showed significant activity against the MDR line A2780AD and the altered β -tubulin-expressing cell lines 1A9PTX10 and 1A9PTX22, suggesting, perhaps, different contact points for the epothilones and Taxol with tubulin (i.e. stronger binding of epothilones around residue 364 than around 270 relative to taxoids).

Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening

The colorimetric cytotoxicity assay used was adapted from Skehan et al (Journal of National Cancer Inst 82:1107-1112, 1990). The procedure provides a rapid, sensitive, and inexpensive method for measuring the cellular protein content of adherent and suspension cultures in 96-well microtiter plates. The method is suitable for ordinary laboratory purposes and for very large-scale applications, such as the National Cancer Institute's disease-oriented in vitro anticancer-drug discovery

screen, which requires the use of several million culture wells per year.

In particular, cultures fixed with trichloroacetic acid were stained for 30 minutes with 0.4% (wt/vol) sulforhodamine B (SRB) dissolved in 1% acetic acid. Unbound dye was removed by four washes with 1% acetic acid, and protein-bound dye was extracted with 10 mM unbuffered Tris base [tris (hydroxymethyl)aminomethane] for determination of optical density in a computer-interfaced, 96-well microtiter plate reader. The SRB assay results were linear with the number of cells and with values for cellular protein measured by both the Lowry and Bradford assays at densities ranging from sparse subconfluence to multilayered supraconfluence. The signal-to-noise ratio, at 564 nm was approximately 1.5 with 1,000 cells per well. The sensitivity of the SRB assay compared favorably with sensitivities of several fluorescence assays and was superior to those of both the Lowry and Bradford assays and to those of 20 other visible dyes.

The SRB assay provides a calorimetric end point that is nondestructive, indefinitely stable, and visible to the naked eye. It provides a sensitive measure of drug-induced cytotoxicity, is useful in quantitating clonogenicity, and is well suited to high-volume, automated drug screening. SRB fluoresces strongly with laser excitation at 488 nm and can be measured quantitatively at the single-cell level by static fluorescence cytometry (Skehan et al (*Journal of National Cancer Inst* 82:1107-1112, 1990)).

Filtration Colorimetric Assay

Microtubule protein (0.25 ml of 1 mg/ml) was placed into an assay tube and 2.5 µl of the test compound were added. The sample was mixed and incubated at 37°C for 30 minutes. Sample (150 µl) was transferred to a well in a 96-well Millipore Multiscreen Durapore hydrophilic 0.22 µm pore size filtration plate which had previously been washed with 200 µl of MEM buffer under vacuum. The well was then washed with 200 µl of MEM buffer.

To stain the trapped protein on the plate, 50 µl amido black solution [0.1% naphthol blue black (Sigma)/45% methanol/ 10% acetic acid] were added to the filter for 2 minutes; then the vacuum was reapplied. Two additions of 200 µl amido black destain solution (90% methanol/2% acetic acid) were added to remove unbound dye. The signal was quantitated by the method of Schaffner and Weissmann et al. *Anal. Biochem.*, 56: 502-514, 1973 as follows:

200 µl of elution solution (25 mM NaOH-0.05 mM EDTA-50% ethanol) were added to the well and the solution was mixed with a pipet after 5 minutes. Following a 10-minutes incubation at room temperature, 150 µl of the elution solution were transferred to the well of a 96-well plate and the absorbance was measured on a Molecular Devices Microplate Reader.

Synthetic Protocols

5 All reactions were carried out under an argon atmosphere
with dry, freshly distilled solvents under anhydrous
conditions, unless otherwise noted. Tetrahydrofuran
(THF), toluene and ethyl ether (ether) were distilled from
sodium-benzophenone, and methylene chloride (Methylene
chloride), from calcium hydride. Anhydrous solvents were
also obtained by passing them through commercially
10 available alumina column. Yields refer to
chromatographically and spectroscopically (¹H NMR)
homogeneous materials, unless otherwise stated. Reagents
were purchased at highest commercial quality and used
without further purification unless otherwise stated.
15 Reactions were monitored by thin layer chromatography
carried out on 0.25 mm E. Merck silica gel plates (60F-
254) using UV light as visualizing agent and 7% ethanolic
phosphomolybdic acid or p-anisaldehyde solution and heat
as developing agents. E. Merck silica gel (60, particle
20 size 0.040-0.063 mm) was used for flash column
chromatography. Preparative thin-layer chromatography
(PTLC) separations were carried out on 0.25, 0.50 or 1 mm
E. Merck silica gel plates (60F-254). NMR spectra were
recorded on Bruker AMX-600 or AMX-500 instruments and
25 calibrated using residual undeuterated solvent as an
internal reference. The following abbreviations were used
to explain the multiplicities: s = singlet, d = doublet,
t = triplet, q = quartet, m = multiplet, b = broad. IR
spectra were recorded on a Perkin-Elmer 1600 series FT-IR

spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with NBA as the matrix. Melting points (mp) are uncorrected and were recorded on a Thomas Hoover Unimelt capillary melting point apparatus.

Synthesis of Sultam 14. Sodium-Mediated Alkylation of *N*-Acylsultam 13 as illustrated in Figure 3. A solution of sodium bis(trimethylsilyl)amide (NaHMDS, 236 mL, 1 M in THF, 1.05 equiv) was added over 30 min at -78 °C to a solution of *N*-acylsultam 13 (synthesized according to Oppolzer et al. Tetrahedron Lett. 1989, 30, 5603-1989; Oppolzer, W. Pure & Appl. Chem. 1990, 62, 1241-1250) (61.0 g, 0.225 mol) in THF (1.1 L, 0.2 M). After stirring the resulting sodium enolate solution at -78 °C for 1 hour, freshly distilled 5-iodo-1-pentene (58 mL, 0.45 mol, 2.0 equiv) in hexamethylphosphoramide (HMPA, 117 mL, 0.675 mol, 3.0 equiv) was added. The reaction mixture was allowed to slowly warm to 25 °C, quenched with water (1.5 L) and extracted with ether (3 x 500 mL). Drying (MgSO₄) and evaporation of the solvents gave crude sultam 14 (76.3 g), which was used without further purification. A pure sample of 14 was obtained by preparative thin layer chromatography (250 mm silica gel plate, 10% EtOAc in hexanes). *R_f* = 0.57 (silica gel, 20% EtOAc in hexanes); [α]_D²⁰ -50.5 (c 2.00, CHCl₃); IR (film) ν_{max} 2939, 1694,

1331, 1216, 1131, 540 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.79-7.72 (m, 1 H, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.00-4.90 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.89 (dd, $J = 7.5, 5.5$ Hz, 1 H, CH_2CHN), 3.50 (d, $J = 14.0$ Hz, 1 H, CH_2SO_2), 3.43 (d, $J = 14.0$ Hz, 1 H, CH_2SO_2), 3.15-3.06 (m, 1 H, $(\text{C}=\text{O})\text{CH}(\text{CH}_3)$), 2.10-2.00 (m, 3 H), 1.96-1.84 (m, 2 H), 1.78-1.68 (m, 1 H), 1.50-1.30 (m, 6 H), 1.16 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.15 (d, $J = 7.5$ Hz, 3 H, CHCH_3), 0.97 (s, 3 H, $\text{C}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 176.4, 138.2, 114.5, 65.1, 53.0, 48.1, 47.6, 44.5, 39.5, 38.5, 34.7, 33.2, 32.7, 26.3, 26.0, 20.7, 19.8, 16.5; HRMS (FAB), calcd for $\text{C}_{18}\text{H}_{30}\text{NO}_3\text{S}$ ($\text{M} + \text{H}^+$) 340.1946, found 340.1942.

Synthesis of Alcohol 15 as illustrated in Figure 3A. (Reductive Cleavage of Sultam 14). A solution of crude sultam 14 (76.0 g, 0.224 mol) in ether (200 mL) was added to a stirred suspension of lithium aluminum hydride (LAH, 9.84 g, 0.246 mol, 1.1 equiv) in ether (900 mL) at -78°C . The reaction mixture was stirred at -78°C for 15 min, quenched by addition of water (9.8 mL) and warmed to 0°C . Sequential addition of 15% aqueous sodium hydroxide solution (9.8 mL) and water (29.4 mL) was followed by warming the reaction mixture to 25°C . After stirring for 5 h, the aluminum salts were removed by filtration through celite, the filtrate was dried (MgSO_4) and the solvent was removed by distillation under atmospheric pressure. Vacuum distillation (bp. $85^\circ\text{C} / 8$ mm Hg) furnished pure alcohol 15 as a colorless oil (17.1 g, 60% from sultam 14). $R_f = 0.40$ (silica gel, 20% EtOAc in hexanes); $[\alpha]_{\text{D}}^{25}$

-11.1 (c 1.41, CHCl₃); IR (film) ν_{max} 3344, 2956, 2927, 2873, 1641, 1460, 1033, 910, 803 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.85-5.77 (m, 1 H, CH₂CH=CH₂), 5.03-4.93 (m, 2 H, CH₂CH=CH₂), 3.53-3.49 (dd, J = 10.5, 6.0 Hz, 1 H, CH₂OH), 3.44-3.41 (dd, J = 10.5, 6.5 Hz, 1 H, CH₂OH), 2.09-2.01 (m, 2 H), 1.67-1.58 (m, 1 H, HOCH₂CH(CH₃)), 1.51-1.34 (m, 3 H), 1.17-1.08 (m, 1 H) 0.92 (d, J = 6.5 Hz, 3 H, CH₃); ¹³C NMR (125.7 MHz, CDCl₃) δ 138.8, 114.2, 68.0, 35.5, 33.9, 32.5, 26.2, 16.4.

Synthesis of Aldehyde 7 as illustrated in Figure 3A. (Oxidation of Alcohol 1)5. To a solution of alcohol 15 (0.768 g, 6.0 mmol) in Methylene chloride (30 mL, 0.2 M) were added powdered 4 Å molecular sieves (1.54 g), 4-methylmorpholine N-oxide (NMO, 1.06 g, 9.0 mmol, 1.5 equiv) and tetrapropylammonium perruthenate (TPAP, 0.105 g, 0.3 mmol, 0.05 equiv) at room temperature. After stirring for 30 min the disappearance of starting material was indicated by TLC. Celite was added (1.54 g) and the suspension was filtered through silica gel and eluted with Methylene chloride. The solvent was carefully distilled off under atmospheric pressure to yield aldehyde 7 (0.721 g, 95%) as a colorless oil. R_f = 0.69 (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{25} +18.3$ (c 2.35, CHCl₃); IR (film) ν_{max} 2934, 1707, 1463, 1238, 912 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.58 (d, 1 H, CHO), 5.80-5.71 (m, 1 H, CH₂CH=CH₂), 5.00-4.90 (m, 2 H, CH₂CH=CH₂), 2.36-2.27 (m, 1 H), 2.10-2.00 (m, 2 H), 1.73-1.65 (m, 1 H), 1.42-1.30 (m, 3 H), 1.06 (d, J = 7.0 Hz, 3 H, CH₃); ¹³C NMR (125.7 MHz,

CDC13) δ 204.9, 138.0, 114.7, 46.0, 33.5, 29.7, 26.0, 13.1.

Synthesis of silyl ether 17a as illustrated in Figure 3B. (Silylation of alcohol 16a). Alcohol 16a (5.0 g, 0.068 mol; glycidol; Aldrich/Sigma) was dissolved in DMF (70 mL, 1.0 M), the solution was cooled to 0 °C and imidazole (9.2 g, 0.135 mol, 2.0 equiv) was added. After stirring for 10 min, tert-butylchlorodiphenylsilane (TPSCl, 24 mL, 0.088 mol, 1.3 equiv) was added and the reaction mixture was allowed to stir for 30 min at 0 °C and for 1 h at 25 °C. Ether (70 mL) was added, followed by saturated aqueous NaHCO₃ solution (70 mL). The organic phase was separated and the aqueous layer was extracted with ether (50 mL), washed with water (2 x 120 mL) and with saturated aqueous NaCl solution (120 mL). The organic extract was dried (MgSO₄), filtered through celite, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc in hexanes) provided silyl ether 17a (18.9 g, 90%). R_f = 0.28 (5% EtOAc in hexanes); [α]_D²⁵ -1.8 (c 1.14, CHCl₃); IR (film) ν_{max} 2957, 2930, 2857, 1471, 1427, 1111, 824, 703 cm⁻¹; ¹H NMR (500 MHz, CDC13) δ 7.72-7.67 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.47-7.38 (m, 6 H, SiC(CH₃)₃(C₆H₅)₂), 3.86 (dd, J = 12.0, 3.0 Hz, 1 H, CH₂OTPS), 3.72 (dd, J = 12.0, 4.5 Hz, 1 H, CH₂OTPS), 3.16-3.12 (m, 1 H, CH₂-O(epoxide)CH), 2.76 (dd, J = 5.0, 4.0, 1 H, CH₂-O(epoxide)CH), 2.62 (dd, J = 5.0, 3.0, 1 H, CH₂-O(epoxide)CH), 1.08 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂); ¹³C NMR

(125.7 MHz, CDCl₃) d 135.5, 133.2, 129.7, 127.6, 64.2, 52.2, 44.3, 26.7, 19.1.

Synthesis of Silyl ether 17b as illustrated in Figure 3B. Silylation of alcohol 16b. Following the procedure described for the synthesis of silyl ether 17a, alcohol 16b (5.0 g, 0.068 mol; Aldrich/Sigma) in DMF (70 mL, 1.0 M) was treated with imidazole (9.2 g, 0.135 mol, 2.0 equiv) and tert-butylchlorodiphenylsilane (24 mL, 0.088 mol, 1.3 equiv) to yield silyl ether 17b (19.8 g, 94%). R_f = 0.28 (5% EtOAc in hexanes); [α]_D²⁵ +2.3 (c 2.00, CHCl₃); IR (film ν_{max} 2957, 2930, 2857, 1471, 1427, 1111, 824, 703 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) d 7.72-7.67 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.47-7.38 (m, 6 H, SiC(CH₃)₃(C₆H₅)₂), 3.86 (dd, J = 12.0, 3.0 Hz, 1 H, CH₂OTPS), 3.72 (dd, J = 12.0, 4.5 Hz, 1 H, CH₂OTPS), 3.16-3.12 (m, 1 H, CH₂-O(epoxide)CH), 2.76 (dd, J = 5.0, 4.0, 1 H, CH₂-O(epoxide)CH), 2.62 (dd, J = 5.0, 3.0, 1 H, CH₂-O(epoxide)CH) 1.08 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂); ¹³C NMR (125.7 MHz, CDCl₃) d 135.5, 133.2, 129.7, 127.6, 64.2, 52.2, 44.3, 26.7, 19.1.

Synthesis of Alcohol 18a as illustrated in Figure 3B. Opening of Epoxide 17a with Vinylcuprate. To a solution of tetravinyltin (3.02 mL, 16.6 mmol, 1.25 equiv) in THF (44 mL) was added n-butyllithium (41.5 mL, 1.6 M in hexanes, 5.0 equiv) at -78 °C and the reaction mixture was stirred for 45 min. The resulting solution of vinylolithium was transferred via cannula to a solution of azeotropically dried (2 x 5 mL toluene) copper(I) cyanide

(2.97 g, 33.2 mmol, 2.5 equiv) in THF (44 mL) at -78 °C, and the mixture was allowed to warm to -30 °C. Epoxide 17a (4.14 g, 13.3 mmol) in THF (44 mL) was transferred via cannula to this vinyl cuprate solution, and the mixture was stirred at -30 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (150 mL), filtered through celite, extracted with ether (2 x 100 mL) and dried (MgSO₄). After removal of the solvents under reduced pressure, flash column chromatography (silica gel, 3% EtOAc in hexanes) furnished alcohol 18a (5.01 g, 86%) as a pale yellow oil. R_f = 0.33 (silica gel, 10% EtOAc in hexanes); [α]_D 22D -2.0 (c 2.20, CHCl₃); IR (film) ν_{max}: 3071, 2930, 2858, 1428, 1111, 703 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.70-7.65 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.47-7.38 (m, 6 H, SiC(CH₃)₃(C₆H₅)₂), 5.84-5.75 (m, 1 H, CH₂CH=CH₂), 5.11-5.04 (m, 2 H, CH₂CH=CH₂), 3.82-3.76 (m, 1 H, CHOH), 3.67 (dd, J = 10.5, 3.5 Hz, 1 H, CH₂OTPS), 3.56 (dd, J = 10.5, 7.0 Hz, 1 H, CH₂OTPS), 2.27-2.22 (m, 2 H, CH₂CH=CH₂), 2.17 (bs, 1 H, OH), 1.08 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 135.6, 135.4, 134.3, 134.3, 133.1, 129.9, 129.7, 127.8, 127.6, 117.4, 71.2, 67.3, 37.5, 26.8, 19.2; HRMS (FAB), calcd for C₂₁H₂₈NaO₂Si (M + Na⁺) 363.1756, found 363.1773.

Synthesis of Alcohol 18b as illustrated in Figure 3B. Opening of Epoxide 17b with Vinylcuprate. Following the procedure described for the synthesis of alcohol 18a, epoxide 17b (1.97 g, 6.3 mmol) yielded alcohol 18b (1.78 g, 83%). R_f = 0.33 (silica gel, 10% EtOAc in hexanes);

[α]_D +2.2 (c 2.00, CHCl₃); IR (film) ν_{max} 3071, 2930, 2858, 1428, 1111, 703 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.70-7.65 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.47-7.38 (m, 6 H, SiC(CH₃)₃(C₆H₅)₂), 5.84-5.75 (m, 1 H, CH₂CH=CH₂), 5.11-5.04 (m, 2 H, CH₂CH=CH₂), 3.82-3.76 (m, 1 H, CHOH), 3.67 (dd, J = 10.5, 3.5 Hz, 1 H, CH₂OTPS), 3.56 (dd, J = 10.5, 7.0 Hz, 1 H, CH₂OTPS), 2.27-2.22 (m, 2 H, CH₂CH=CH₂), 2.17 (bs, 1 H, OH), 1.08 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 135.6, 135.4, 134.3, 134.3, 133.1, 129.9, 129.7, 127.8, 127.6, 117.4, 71.2, 67.3, 37.5, 26.8, 19.2; HRMS (FAB), calcd for C₂₁H₂₈NaO₂Si (M + Na⁺) 363.1756, found 363.1773.

Synthesis of Keto Ester 20 as illustrated in Figure 3C. Horner-Wadsworth-Emmons Reaction of Aldehyde 12 with Phosphonate 19. A solution of phosphonate 19 (23.6 g, 94 mmol, 1.2 equiv; Aldrich) in THF (100 mL) was transferred via cannula to a suspension of sodium hydride (60 % dispersion in mineral oil, 5.0 g, 125 mmol, 1.6 equiv) in THF (200 mL) at 25 °C. After stirring for 15 min, the reaction mixture was cooled to 0 °C, and a solution of aldehyde 12 (10.0 g, 78 mmol; synthesized according to Inuka, T.; Yoshizawa, R. J. Org. Chem. 1967, 32, 404-407) in THF (20 mL) was added via cannula and the ice-bath was removed. After 1 h at 25 °C, TLC indicated the disappearance of aldehyde 12. The mixture was then separated between water (320 mL) and hexanes (100 mL). The aqueous layer was extracted with hexanes (100 mL) and the combined organic layers were successively washed with

water (200 mL) and saturated aqueous NaCl solution (200 mL). Drying (MgSO₄), concentration under reduced pressure and purification by flash column chromatography (silica gel, 10% EtOAc in hexanes) yielded keto ester 20 (17.4 g, 99%) as a yellow oil. R_f = 0.58 (silica gel, 20% EtOAc in hexanes); IR (film) ν_{max} 2977, 1714, 1645, 1318, 1297, 1158 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.91 (d, J = 15.5 Hz, 1 H, CH=CHCOO), 5.77 (d, J = 15.5 Hz, 1 H, CH=CHCOO), 2.47 (q, J = 7.0 Hz, 2 H, CH₂CH₃), 1.47 (s, 9 H, C(CH₃)₃), 1.25 (s, 6 H, C(CH₃)₂), 0.99 (t, J = 7.0 Hz, 3 H, CH₂CH₃); ¹³C NMR (125.7 MHz, CDCl₃) δ 211.7, 165.5, 150.3, 122.2, 80.5, 50.2, 31.2, 28.0, 23.5, 7.9; HRMS (FAB), calcd for C₁₃H₂₃O₃ (M + H⁺) 227.1647, found 227.1656.

Synthesis of Keto Acid 21 as illustrated in Figure 3C. Hydrolysis of Keto Ester 20. Keto ester 20 (17.4 g, 77 mmol) in Methylene chloride (39 mL, 2 M) was treated with trifluoroacetic acid (TFA, 39 mL, 2 M) at 25 °C. Within 30 minutes TLC indicated disappearance of the ester. The mixture was concentrated under reduced pressure, dissolved in saturated aqueous NaHCO₃ solution (20 mL) and washed with ether (2 x 20 mL). The aqueous phase was then acidified to pH ~ 2 with 4 N HCl, saturated with NaCl, and extracted with EtOAc (6 x 20 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give pure keto acid 21 (13.0 g, 99%) as a clear oil, which solidified on standing. R_f = 0.20 (silica gel, 2% TFA in Methylene chloride); mp 56-57 °C (EtOAc); IR (film) ν_{max} 2979, 1712, 1647, 1300, 1201 cm⁻¹;

1H NMR (500 MHz, CDCl₃) δ 7.18 (d, J = 16.0 Hz, 1 H, CH=CHCOOH), 5.89 (d, J = 16.0 Hz, 1 H, CH=CHCOOH), 2.50 (q, J = 7.0 Hz, 2 H, CH₂CH₃), 1.31 (s, 6 H, C(CH₃)₂), 1.03 (t, J = 7.0 Hz, 3 H, CH₂CH₃); ¹³C NMR (125.7 MHz, CDCl₃) δ 211.8, 171.3, 154.3, 119.6, 50.4, 31.2, 23.2, 7.7; HRMS (FAB), calcd for C₉H₁₄NaO₃ (M + Na⁺) 193.0841, found 193.0846.

Synthesis of Keto Ester 22a as illustrated in Figure 4. EDC Coupling of Alcohol 18a with Keto Acid 21. A solution of keto acid 21 (2.43 g, 14.3 mmol, 1.2 equiv), 4-(dimethylamino)pyridine (4-DMAP, 0.145 g, 1.2 mmol, 0.1 equiv) and alcohol 18a (4.048 g, 11.9 mmol, 1.0 equiv) in Methylene chloride (40 mL, 0.3 M) was cooled to 0 °C and then treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 2.74 g, 14.3 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The solution was concentrated to dryness in vacuo, and the residue was taken up in EtOAc (10 mL) and water (10 mL). The organic layer was separated, washed with saturated NH₄Cl solution (10 mL) and water (10 mL) and dried (MgSO₄). Evaporation of the solvents followed by flash column chromatography (silica gel, 4% EtOAc in hexanes) resulted in pure keto ester 22a (5.037 g, 86%). R_f = 0.41 (silica gel, 10% EtOAc in hexanes); [α]_D²⁵ -6.1 (c 1.22, CHCl₃); IR (film) ν_{max} 3072, 2960, 2933, 2858, 1715, 1645, 1470, 1428, 1295, 1181, 1112, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.66-7.64 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.44-7.36

(m, 6 H, SiC(CH₃)₃(C₆H₅)₂), 7.05 (d, 1 H, J = 16.0 Hz, CH=CHCOO), 5.86 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.79-5.70 (m, 1 H, CH₂CH=CH₂), 5.15-5.04 (m, 3 H, CH₂CH=CH₂ and CO₂CH), 3.76-3.70 (m, 2 H, CH₂OTPS), 2.53-2.36 (m, 4 H), 1.29 (s, 6 H, C(CH₃)₂), 1.04 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂), 1.01 (t, J = 7.0 Hz, 3 H, CH₃CH₂C=O); ¹³C NMR (125.7 MHz, CDCl₃) δ 211.4, 165.7, 151.7, 135.5, 135.4, 133.2, 129.6, 127.6, 120.6, 117.9, 73.6, 64.3, 50.4, 35.0, 31.3, 26.6, 23.6, 23.5, 19.2, 7.9; HRMS (FAB), calcd for C₃₀H₄₀OsO₄Si (M + Cs⁺) 625.1750, found 625.1765.

Synthesis of Dienes 23 and 24 as illustrated in Figure 4. Aldol Condensation of Ester 22a with Aldehyde 7. A solution of keto ester 22a (1.79 g, 3.63 mmol, 1.0 equiv) in THF (15 mL) was added via cannula to a freshly prepared solution of lithium diisopropylamide [LDA; formed by addition of n-BuLi (2.83 mL, 1.6 M solution in hexanes, 4.58 mmol, 1.25 equiv) to a solution of diisopropylamine (0.61 mL, 4.36 mmol, 1.2 equiv) in THF (30 mL) at -10 °C and stirring for 30 min] at -78 °C. After 15 min the reaction mixture was allowed to warm to -40 °C and was stirred for 45 min. The reaction mixture was cooled to -78 °C and a solution of aldehyde 7 (0.740 g, 5.8 mmol, 1.6 equiv) in THF (15 mL) was added dropwise. The resulting mixture was stirred for 15 min, then warmed to -40 °C for 30 min, cooled back to -78 °C and then quenched by slow addition of saturated aqueous NH₄Cl solution (10 mL). The reaction mixture was warmed to 25 °C, diluted with EtOAc (10 mL) and the aqueous phase was extracted with EtOAc (3

x 10 mL). The combined organic layers were dried (MgSO₄), concentrated under reduced pressure and subjected to flash chromatographic purification (silica gel, 5 & 20% EtOAc in hexanes) to afford a mixture of aldol products 23 (926 mg, 42%) and 24 (724 mg, 33%), along with unreacted starting keto ester 22a (178 mg, 10%). 23: R_f = 0.40 (silica gel, 18% EtOAc in hexanes); [α]_D²⁵ -11.4 (c 1.00, CHCl₃); IR (film) ν_{max} 3518, 2962, 2932, 2858, 1722, 1644, 1294, 1182, 1114, 989, 702 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.67-7.63 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.45-7.40 (m, 2 H, SiC(CH₃)₃(C₆H₅)₂), 7.40-7.35 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.03 (d, 1 H, J = 15.8 Hz, CH=CHCOO), 5.92 (d, J = 15.8 Hz, 1 H, CH=CHCOO), 5.84-5.76 (m, 1 H, CH₂CH=CH₂), 5.76-5.68 (m, 1 H, CH₂CH=CH₂), 5.14-5.09 (m, 1 H, CO₂CH), 5.08 (d, J = 17.2 Hz, 1 H, CH₂CH=CH₂), 5.04 (d, J = 10.1 Hz, 1 H, CH₂CH=CH₂), 4.99 (d, J = 18.9 Hz, 1 H, CH₂CH=CH₂), 4.92 (d, J = 10.2 Hz, 1 H, CH₂CH=CH₂), 3.76-3.69 (m, 2 H, CH₂OTPS), 3.29 (d, J = 8.9 Hz, 1 H, CHOH(CHCH₃)), 3.16 (s, 1 H, CHOH(CHCH₃)), 3.13 (qd, J = 7.0, 1.8 Hz, 1 H, CH₃CH(C=O)), 2.52-2.45 (m, 1 H), 2.42-2.35 (m, 1 H), 2.09-1.97 (m, 2 H), 1.76-1.68 (m, 1 H), 1.52-1.43 (m, 2 H), 1.30 (s, 3 H, C(CH₃)₂), 1.30 (s, 3 H, C(CH₃)₂), 1.30-1.25 (m, 1 H), 1.12-1.00 (m, 1 H), 1.03 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂), 1.01 (d, J = 7.1 Hz, 3 H, CH₃CH(C=O)), 0.77 (d, J = 6.8 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 217.0, 165.2, 150.1, 138.9, 135.4, 135.4, 135.4, 133.1, 133.1, 129.6, 129.6, 127.6, 127.5, 121.5, 117.9, 114.2, 74.9, 73.8, 64.4, 51.6, 41.5, 35.5, 35.2, 34.3, 32.2, 26.8, 26.2, 23.3, 23.3, 19.4, 15.6, 10.4; HRMS (FAB), calcd for

C₃₈H₅₄CsO₅Si (M + Cs⁺) 751.2795, found 751.2766. 24: R_f =
 0.30 (silica gel, 18% EtOAc in hexanes); [α]_D²² -1.33 (c
 0.60, CHCl₃); IR (film) ν_{max} 3521, 2962, 2932, 2858, 1722,
 1644, 1294, 1182, 1113, 988, 702 cm⁻¹; ¹H NMR (600 MHz,
 CDCl₃) δ 7.68-7.63 (m, 4 H, SiPh₂), 7.45-7.40 (m, 2 H,
 SiC(CH₃)₃(C₆H₅)₂), 7.40-7.35 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂),
 7.03 (d, 1 H, J = 15.8 Hz, CH=CHCOO), 5.90 (d, J = 15.8 Hz,
 1 H, CH=CHCOO), 5.82-5.68 (m, 2 H, 2 × CH₂CH=CH₂), 5.14-
 5.08 (m, 1 H, CO₂CH), 5.09 (d, J = 16.9 Hz, 1 H,
 CH₂CH=CH₂), 5.05 (d, J = 10.1 Hz, 1 H, CH₂CH=CH₂), 4.99 (d,
 J = 17.1 Hz, 1 H, CH₂CH=CH₂), 4.95 (d, J = 10.1 Hz, 1 H,
 CH₂CH=CH₂), 3.76-3.69 (m, 2 H, CH₂OTPS), 3.44 (dd, J =
 6.6, 3.9 Hz, 1 H, CHOH(CHCH₃)), 3.13-3.08 (m, 1 H,
 CH₃CH(C=O)), 2.69 (bs, 1 H, CHOH(CHCH₃)), 2.53-2.47 (m, 1
 H), 2.43-2.37 (m, 1 H), 2.07-1.95 (m, 2 H), 1.48-1.25 (m,
 5 H), 1.31 (s, 3 H, C(CH₃)₂), 1.29 (s, 3 H, C(CH₃)₂), 1.05
 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.03 (s, 9 H,
 SiC(CH₃)₃(C₆H₅)₂), 0.92 (d, J = 6.6 Hz, 3 H, CH₃CHCH₂);
¹³C NMR (150.9 MHz, CDCl₃) δ 216.1, 165.2, 150.3, 138.5,
 135.5, 135.4, 135.4, 133.1, 133.1, 129.6, 129.6, 127.6,
 127.6, 121.4, 117.9, 114.6, 75.1, 73.8, 64.4, 51.5, 42.6,
 35.5, 35.1, 33.9, 32.6, 26.8, 26.0, 23.6, 23.3, 19.4,
 15.0, 12.3; HRMS (FAB), calcd for C₃₈H₅₄CsO₅Si (M + Cs⁺)
 751.2795, found 751.2771.

**Synthesis of Hydroxy Lactone 25 as illustrated in
 Figure 4. Olefin Metathesis of Diene 23.** To a solution
 of diene 23 (0.186 g, 0.3 mmol) in Methylene chloride (100
 mL, 0.003 M) was added

bis(tricyclohexylphosphine)benzylidene ruthenium
 dichloride ($\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$, 25 mg, 0.03 mol, 0.1
 equiv; available from Aldrich) and the reaction mixture
 was allowed to stir at 25 °C for 12 h. After the
 5 completion of the reaction was established by TLC, the
 solvent was removed under reduced pressure and the crude
 product was purified by flash chromatography (silica gel,
 30% EtOAc in hexanes) to give trans-hydroxy lactone 25
 (151 mg, 85%). $R_f = 0.50$ (silica gel, 30% EtOAc in
 10 hexanes); $[\alpha]_{22D} +65.9$ (c 0.80, CHCl_3); IR (film) ν_{max}
 3520, 2960, 2932, 2858, 1711, 1705, 1646, 1292, 1183,
 1114, 982, 702, 505 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.69-
 7.64 (m, 4 H, $\text{SiC}(\text{CH}_3)_3(\text{C}_6\text{H}_5)_2$), 7.46-7.36 (m, 6 H,
 $\text{SiC}(\text{CH}_3)_3(\text{C}_6\text{H}_5)_2$), 6.78 (d, $J = 15.5$ Hz, 1 H, $\text{CH}=\text{CHCOO}$),
 15 5.98 (d, $J = 15.5$ Hz, 1 H, $\text{CH}=\text{CHCOO}$), 5.40 (ddd, $J = 15.5$,
 8.5, 4.0 Hz, 1 H, $\text{CH}=\text{CHCH}_2$), 5.38 (ddd, $J = 15.5$, 8.5, 4.5
 Hz, 1 H, $\text{CH}=\text{CHCH}_2$), 5.22-5.16 (m, 1 H, CO_2CH), 3.75 (dd, J
 = 10.5, 6.0 Hz, 1 H, CH_2OTPS), 3.70 (dd, $J = 10.5$, 5.0 Hz,
 1 H, CH_2OTPS), 3.58 (bs, 1 H, $\text{CHOH}(\text{CHCH}_3)$), 3.05 (qd, $J =$
 20 6.5, 5.5 Hz, 1 H, $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 2.42 (d, $J = 14.0$ Hz, 1 H),
 2.24-2.16 (m, 2 H), 2.12-2.04 (m, 1 H), 2.03-1.94 (m, 1
 H), 1.55-1.40 (m, 2 H), 1.37 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.28-1.04
 (m, 3 H), 1.20 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.15 (d, $J = 7.0$ Hz, 3
 H, $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 1.05 (s, 9 H, $\text{SiC}(\text{CH}_3)_3(\text{C}_6\text{H}_5)_2$), 0.93 (d,
 25 $J = 7.0$ Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, CDCl_3) δ
 214.8, 164.9, 149.6, 135.5, 135.4, 133.2, 133.2, 132.7,
 129.6, 129.6, 127.6, 127.6, 126.3, 122.5, 75.7, 73.2,
 65.6, 52.2, 42.1, 38.2, 34.8, 33.2, 30.3, 27.2, 26.9,
 23.4, 23.2, 19.4, 16.3, 14.6; HRMS (FAB), calcd for

C36H50O5CsSi (M + Cs+) 723.2482, found 723.2508.

Synthesis of Hydroxy Lactone 26 as illustrated in Figure 4. Olefin Metathesis of Diene 24. Following the procedure described above for the synthesis of hydroxy lactone 25, a solution of diene 24 (0.197 g, 0.32 mmol) in Methylene chloride (100 mL, 0.003 M) was treated with bis(tricyclohexylphosphine)benzylidene ruthenium dichloride ((RuCl₂(=CHPh)(PCy₃)₂, 26 mg, 0.032 mol, 0.1 equiv), to produce, after flash chromatography (silica gel, 18 & 25% EtOAc in hexanes), trans-hydroxy lactone 26 (150 mg, 79%). R_f = 0.3 (silica gel, 18% EtOAc in hexanes); [α]_D²² -3.00 (c = 0.40, CHCl₃); IR (film) ν_{max} 3522, 2961, 2931, 2857, 1718, 1698, 1646, 1294, 1182, 1113, 702 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.67-7.63 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.45-7.41 (m, 2 H, SiC(CH₃)₃(C₆H₅)₂), 7.40-7.36 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.07 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.86 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.30 (ddd, J = 15.2, 7.4, 4.2 Hz, 1 H, CH=CHCH₂), 5.28 (ddd, J = 15.2, 7.5, 4.2 Hz, 1 H, CH=CHCH₂), 5.26-5.21 (m, 1 H, CO₂CH), 3.77 (dd, J = 10.7, 6.3 Hz, 1 H, CH₂OTPS), 3.70 (dd, 1 H, J = 10.7, 5.2 Hz, CH₂OTPS), 3.27 (d, J = 9.0, 1 H, CHOH(CHCH₃)), 3.13 (q, J = 6.9 Hz, 1 H, CH₃CH(C=O)), 2.87 (bs, 1 H, CHOH(CHCH₃)), 2.52-2.45 (m, 1 H), 2.34-2.26 (m, 1 H), 2.15-2.08 (m, 1 H), 1.97-1.89 (m, 1 H), 1.52-1.44 (m, 1 H), 1.40-1.31 (m, 1 H), 1.31 (s, 3 H, C(CH₃)₂), 1.30-1.20 (m, 1 H), 1.24 (s, 3 H, C(CH₃)₂), 1.12-1.00 (m, 1 H), 1.04 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂), 1.01 (d, 3 H, J = 6.9 Hz, CH₃CH(C=O)).

0.96 (d, 3 H, $J = 6.6$ Hz, CH_3CHCH_2), 0.93 (m, 1 H); ^{13}C -NMR (150.9 MHz, CDCl_3) δ 217.8, 165.3, 151.1, 135.5, 135.4, 133.3, 133.2, 133.1, 129.6, 129.6, 127.6, 127.6, 125.6, 121.5, 75.0, 73.4, 64.9, 51.0, 43.6, 35.6, 34.2, 32.7, 32.0, 26.9, 25.6, 25.2, 24.0, 19.4, 16.0, 7.0; HRMS (FAB), calcd for $\text{C}_{36}\text{H}_{50}\text{O}_5\text{CsSi}$ ($M + \text{Cs}^+$) 723.2482, found 723.2506.

Synthesis of Diol 27 as illustrated in Figure 4.

Desilylation of TPS Ether 25. A solution of TPS ether 25 (145 mg, 0.23 mmol) in THF (4.7 mL, 0.05 M) was treated with glacial acetic acid (70 mL, 1.15 mmol, 5.0 equiv) and tetrabutylammonium fluoride (TBAF, 490 mL, 1 M solution in THF, 0.46 mmol, 2.0 equiv) at 25 °C. After stirring for 36 h, no starting material was detected by TLC and the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL). Extractions with ether (3 x 10 mL), drying (MgSO_4) and concentration was followed by flash chromatographic purification (silica gel, 50% EtOAc in hexanes) to provide diol 27 (78 mg, 92%). $R_f = 0.30$ (silica gel, ether), $[\alpha]_{22D} +144.5$ (c 0.51, CHCl_3); IR (film) ν_{max} 3440, 2933, 1706, 1646, 1293, 1183, 982 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.82 (d, $J = 16.0$ Hz, 1 H, $\text{CH}=\text{CHCOO}$), 6.08 (d, $J = 16.0$ Hz, 1 H, $\text{CH}=\text{CHCOO}$), 5.42 (ddd, $J = 15.5, 8.0, 4.5$ Hz, 1 H, $\text{CH}=\text{CHCH}_2$), 5.40 (ddd, $J = 15.5, 8.5, 4.5$ Hz, 1 H, $\text{CH}=\text{CHCH}_2$), 5.20-5.14 (m, 1 H, CO_2CH), 3.76 (dd, $J = 12.0, 4.0$ Hz, 1 H, CH_2OH), 3.72 (dd, $J = 12.0, 6.5$ Hz, 1 H, CH_2OH), 3.58 (dd, $J = 5.0, 2.5$ Hz, 1 H, $\text{CHOH}(\text{CHCH}_3)$), 3.06 (qd, $J = 7.0, 6.0$ Hz, 1 H,

CH₃CH(C=O)), 2.38-2.34 (m, 1 H), 2.28-2.20 (m, 1 H), 2.12-2.03 (m, 1 H), 2.03-1.95 (m, 1 H), 1.55-1.42 (m, 2 H), 1.40 (s, 3 H, C(CH₃)₂), 1.22-1.08 (m, 2 H), 1.22 (s, 3 H, C(CH₃)₂), 1.15 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.08-0.86 (m, 1 H), 0.94 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); ¹³C-NMR (125.7 MHz, CDCl₃) δ 214.8, 165.3, 150.4, 133.0, 126.0, 122.1, 75.5, 73.7, 64.9, 52.1, 41.9, 38.0, 34.4, 33.0, 30.1, 26.9, 23.2, 22.7, 16.1, 14.6; HRMS (FAB), calcd for C₂₀H₃₃O₅ (M + H⁺) 353.2328, found 353.2319.

Synthesis of Diol 28 as illustrated in Figure 4.
 Desilylation of TPS Ether 26. In accordance with the procedure describing the desilylation of TPS ether 25, a solution of TPS ether 26 (31 mg, 0.05 mmol) in THF (1.0 mL, 0.05 M) was treated with glacial acetic acid (15 mL, 0.25 mmol, 5.0 equiv) and tetrabutylammonium fluoride (TBAF, 105 mL, 1 M solution in THF, 0.10 mmol, 2.0 equiv) to yield diol 28 (17 mg, 95%) as a crystalline solid. R_f = 0.15 (silica gel, 50% EtOAc in hexanes); mp 128-129 °C (EtOAc-hexanes); [α]_D²⁵ +45.6 (c 0.80, CHCl₃); IR (film) ν_{max} 3442, 2932, 1702, 1647, 1296, 1184, 974 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.14 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.94 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.34 (ddd, J = 15.4, 7.6, 4.2 Hz, 1 H, CH=CHCH₂), 5.32 (ddd, J = 15.4, 7.6, 4.2 Hz, 1 H, CH=CHCH₂), 5.20-5.16 (m, 1 H, CO₂CH), 3.75-3.73 (m, 2 H, CH₂OH), 3.28 (dd, J = 9.0, 1.2 Hz, 1 H, CHOH(CHCH₃)), 3.13 (qd, J = 7.0, 1.2 Hz, 1 H, CH₃CH(C=O)), 2.81 (bs, 1 H, CHOH(CHCH₃)), 2.46-2.42 (m, 1 H), 2.36-2.30 (m, 1 H), 2.17-2.13 (m, 1 H), 1.97-1.92 (m, 1 H), 1.86

(bs, 1 H, CH₂OH), 1.51-1.46 (m, 1 H), 1.40-1.22 (m, 2H), 1.33 (s, 3 H, C(CH₃)₂), 1.27 (s, 3 H, C(CH₃)₂), 1.12-0.89 (m, 2 H) 1.01 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 0.96 (d, J = 6.6 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 217.4, 165.8, 151.9, 133.6, 125.3, 121.2, 75.0, 74.4, 64.7, 51.0, 43.8, 35.6, 34.3, 32.7, 32.0, 25.5, 25.3, 24.0, 16.0, 9.9; HRMS (FAB), calcd for C₂₀H₃₃O₅ (M + H⁺) 353.2328, found 353.2323.

Synthesis of Ester 22b as illustrated in Figure 5.
 DCC Coupling of Alcohol 18b with Keto Acid 21. To a solution of alcohol 18b (1.000 g, 2.94 mmol, 1.0 equiv), 1,3-dicyclohexylcarbodiimide (DCC, 0.836 g, 4.06 mmol, 1.4 equiv) and 4-dimethylaminopyridine (4-DMAP, 0.496 g, 4.06 mmol, 1.4 equiv) in toluene (30 mL, 0.1 M) was added keto acid 21 (0.638 g, 3.75 mmol, 1.2 equiv) at 25 °C. After 12 h the reaction was complete, as indicated by TLC. The reaction mixture was then passed through a short plug of silica gel, eluted with toluene and concentrated under reduced pressure. The crude material was submitted to flash column chromatography (silica gel, 5% EtOAc in hexanes) to yield pure 22b (1.38 g, 95%). R_f = 0.50 (silica gel, 17% EtOAc in hexanes); [α]_D²⁰ +7.2 (c 2.00, CHCl₃); IR (film) ν_{max} 3072, 2960, 2933, 2858, 1715, 1645, 1470, 1428, 1295, 1181, 1112, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.66-7.64 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.44-7.36 (m, 6 H, SiC(CH₃)₃(C₆H₅)₂), 7.05 (d, 1 H, J = 16.0 Hz, CH=CHCOO), 5.86 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.79-5.70 (m, 1 H, CH₂CH=CH₂), 5.15-5.04 (m, 3 H, CH₂CH=CH₂ and

CO₂CH), 3.76-3.70 (m, 2 H, CH₂OTPS), 2.53-2.36 (m, 4 H),
 1.29 (s, 6 H, C(CH₃)₂), 1.04 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂),
 1.01 (t, J = 7.0 Hz, 3 H, CH₃CH(C=O)); ¹³C NMR (125.7 MHz,
 CDC13) δ 211.4, 165.7, 151.7, 135.5, 135.4, 133.2, 129.6,
 127.6, 120.6, 117.9, 73.6, 64.3, 50.4, 35.0, 31.3, 26.6,
 23.6, 23.5, 19.2, 7.9; HRMS (FAB), calcd for C₃₀H₄₀O₄Si
 (M + Cs⁺) 625.1750, found 625.1775.

Synthesis of dienes 29 and 30 as illustrated in
Figure 5. Aldol Condensation of Ester 22b with Aldehyde
7. In accordance with the procedure described for the
 preparation of dienes 23 and 24, keto ester 22b (0.702 g,
 1.43 mmol, 1.0 equiv) in THF (8.0 mL) was treated with
 lithium diisopropylamide [LDA; freshly prepared from n-
 butyllithium (1.12 mL, 1.6 M solution in hexanes, 1.79
 mmol, 1.25 equiv) and diisopropylamine (241 mL, 1.72 mmol,
 1.2 equiv) in THF (16 mL)] and aldehyde 7 (289 mg, 2.29
 mmol, 1.6 equiv) in THF (3.0 mL) to afford a mixture of
 aldol products 29 (0.478 g, 54%) and 30 (0.210 g, 24%) and
 along with unreacted starting material 22b (79 mg, 11%).
 29: R_f = 0.39 (silica gel, 17% EtOAc in hexanes); [α]_D²⁵
 -6.0 (c 0.30, CHCl₃); IR (film) ν_{max} 2962, 2931, 2858,
 1722, 1698, 1294, 1182, 1114, 990, 702 cm⁻¹; ¹H NMR (600
 MHz, CDC13) δ 7.66-7.62 (m, 4 H, SiPh₂), 7.45-7.40 (m, 2
 H, SiC(CH₃)₃(C₆H₅)₂), 7.40-7.35 (m, 4 H,
 SiC(CH₃)₃(C₆H₅)₂), 7.03 (d, 1 H, J = 16.0 Hz, CH=CHCOO),
 5.90 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.84-5.76 (m, 1 H,
 CH₂CH=CH₂), 5.76-5.68 (m, 1 H, CH₂CH=CH₂), 5.14-5.08 (m, 1
 H, CO₂CH), 5.09 (d, J = 17.9 Hz, 1 H, CH₂CH=CH₂), 5.06 (d,

J = 10.3 Hz, 1 H, CH₂CH=CH₂), 4.99 (d, J = 17.1 Hz, 1 H, CH₂CH=CH₂), 4.93 (d, J = 10.2 Hz, 1 H, CH₂CH=CH₂), 3.76-3.69 (m, 2 H, CH₂OTPS), 3.30 (d, J = 8.8 Hz, 1 H, CHOH(CHCH₃)), 3.17 (s, 1 H, CHOH(CHCH₃)), 3.12 (q, J = 7.0 Hz, 1 H, CH₃CH(C=O)), 2.52-2.46 (m, 1 H), 2.42-2.36 (m, 1 H), 2.09-1.98 (m, 2 H), 1.76-1.68 (m, 1 H), 1.52-1.43 (m, 2 H), 1.31 (s, 3 H, C(CH₃)₂), 1.29 (s, 3 H, C(CH₃)₂), 1.30-1.25 (m, 1 H), 1.12-1.05 (m, 1 H), 1.03 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂), 1.00 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 0.77 (d, J = 6.7 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 217.0, 165.2, 150.1, 138.9, 135.4, 135.4, 135.4, 133.1, 133.1, 129.6, 129.6, 127.6, 127.6, 121.5, 117.9, 114.2, 75.0, 73.9, 64.4, 51.5, 41.6, 35.5, 35.1, 34.3, 32.2, 26.8, 26.2, 23.5, 23.2, 19.4, 15.6, 10.4; HRMS (FAB), calcd for C₃₈H₅₄O₅Si (M + Cs⁺) 751.2795, found 751.2761. 30: R_f = 0.28 (silica gel, 17% EtOAc in hexanes); [α]_D²⁵ +6.2 (c 1.00, CHCl₃); IR (film) ν_{max} 2962, 2932, 2858, 1722, 1644, 1294, 1182, 1114, 988, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.68-7.63 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.45-7.40 (m, 2 H, SiC(CH₃)₃(C₆H₅)₂), 7.40-7.35 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.03 (d, 1 H, J = 16.0 Hz, CH=CHCOO), 5.92 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.83-5.68 (m, 2 H, 2 x CH₂CH=CH₂), 5.14-5.09 (m, 1 H, CO₂CH), 5.09 (d, J = 18.5 Hz, 1 H, CH₂CH=CH₂), 5.04 (d, J = 10.5 Hz, 1 H, CH₂CH=CH₂), 4.99 (d, J = 17.5 Hz, 1 H, CH₂CH=CH₂), 4.94 (d, J = 10.0 Hz, 1 H, CH₂CH=CH₂), 3.77-3.69 (m, 2 H, CH₂OTPS), 3.43 (dd, J = 6.5, 4.0 Hz, 1 H, CHOH(CHCH₃)), 3.14-3.07 (m, 1 H, CH₃CH(C=O)), 2.70 (bs, 1 H, CHOH(CHCH₃)), 2.53-2.46 (m, 1 H), 2.43-2.36 (m, 1 H).

2.07-1.95 (m, 2 H), 1.48-1.00 (m, 5 H), 1.30 (s, 3 H, C(CH₃)₂), 1.30 (s, 3 H, C(CH₃)₂), 1.05 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.04 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂), 0.91 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 216.4, 165.4, 150.4, 138.7, 135.6, 135.5, 135.5, 133.3, 133.2, 129.7, 129.7, 127.7, 127.7, 121.4, 118.0, 114.6, 75.0, 73.8, 64.3, 51.5, 42.4, 35.4, 35.1, 33.8, 32.5, 26.7, 25.9, 23.3, 19.2, 14.8, 12.2; HRMS (FAB), calcd for C₃₈H₅₄CsO₅Si (M + Cs⁺) 751.2795, found 751.2770.

Synthesis of Hydroxy Lactone 31 as illustrated in Figure 5. Olefin Metathesis of Diene 29. A solution of diene 29 (104 mg, 0.17 mmol) in Methylene chloride (25 mL, 0.007 M) was treated with bis(tricyclohexylphosphine)benzylidene ruthenium dichloride ((RuCl₂(=CHPh)(PCy₃)₂, 14 mg, 0.017 mmol, 0.1 equiv; Aldrich), in accordance with the procedure described for the preparation of hydroxy lactone 25, to furnish, after flash column chromatography (silica gel, 5 & 17% EtOAc in hexanes), hydroxy lactone 31 (79 mg, 80%). R_f = 0.18 (silica, 20% EtOAc in hexanes); [α]_D²⁵ +37.5 (c = 0.50, CHCl₃); IR (film) ν_{max} 3519, 2961, 2931, 2857, 1719, 1698, 1644, 1292, 1185, 1113 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.67-7.62 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.45-7.41 (m, 2 H, SiC(CH₃)₃(C₆H₅)₂), 7.41-7.36 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.02 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.83 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.34 (ddd, J = 15.7, 7.4, 4.7 Hz, 1 H, CH=CHCH₂), 5.32 (ddd, J = 15.7, 8.0, 3.8 Hz, 1 H, CH=CHCH₂), 5.26-5.21 (m, 1 H, CO₂CH), 3.74 (dd, J

= 10.8, 6.1 Hz, 1 H, CH₂OTPS), 3.68 (dd, 1 H, J = 10.8, 4.8 Hz, CH₂OTPS), 3.58 (bs, 1 H, CHOH(CHCH₃)), 3.04 (qd, J = 6.8, 2.7 Hz, 1 H, CH₃CH(C=O)), 2.49-2.41 (m, 2 H), 2.30-2.22 (m, 1 H), 2.17-2.10 (m, 1 H), 1.92-1.83 (m, 1 H), 1.65-1.50 (m, 2 H), 1.35 (s, 3 H, C(CH₃)₂), 1.21 (s, 3 H, C(CH₃)₂), 1.30-1.00 (m, 3 H), 1.11 (d, 3 H, J = 6.7 Hz, CH₃CH(C=O)), 1.03 (s, 9 H, SiC(CH₃)₃(C₆H₅)₂), 0.92 (d, 3 H, J = 7.0 Hz, CH₃CHCH₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 216.4, 165.3, 150.7, 135.4, 135.4, 133.6, 133.2, 133.1, 129.6, 129.6, 127.6, 127.6, 125.7, 122.0, 74.3, 73.5, 65.3, 51.1, 43.0, 38.3, 34.4, 31.9, 31.4, 26.8, 26.8, 25.0, 23.6, 19.4, 15.3, 12.9; HRMS (FAB), calcd for C₃₆H₅₀O₅CsSi (M + Cs⁺) 723.2482, found 723.2506.

Synthesis of Hydroxy Lactone 32 as illustrated in Figure 5. Olefin Metathesis of Diene 30. A solution of diene 30 (20 mg, 0.03 mmol) in Methylene chloride (10 mL, 0.003 M) was treated with bis(tricyclohexylphosphine)benzylidene ruthenium dichloride ((RuCl₂(=CHPh)(PCy₃)₂, 2.5 mg, 0.003 mmol, 0.1 equiv; Aldrich), in accordance with the procedure described for the preparation of hydroxy lactone 25, to produce after preparative thin layer chromatography (250 mm silica gel plate, 10% EtOAc in hexanes) hydroxy lactone 32 (15 mg, 81%). R_f = 0.34 (silica gel, 17% EtOAc in hexanes); [α]_D²⁵ -90.0 (c 0.60, CHCl₃); IR (film) ν_{max} 3524, 2960, 2931, 2856, 1722, 1698, 1294, 1185, 1113, 988, 702, 505 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.67-7.64 (m, 4 H, SiC(CH₃)₃(C₆H₅)₂), 7.45-7.41 (m, 2 H,

$\text{SiC}(\text{CH}_3)_3(\text{C}_6\text{H}_5)_2$, 7.40-7.36 (m, 4 H, $\text{SiC}(\text{CH}_3)_3(\text{C}_6\text{H}_5)_2$),
 6.91 (d, $J = 15.8$ Hz, 1 H, $\text{CH}=\text{CHCOO}$), 5.98 (d, $J = 15.8$
 Hz, 1 H, $\text{CH}=\text{CHCOO}$), 5.36 (ddd, $J = 15.4, 7.3, 4.6$ Hz, 1 H,
 $\text{CH}=\text{CHCH}_2$), 5.35 (ddd, $J = 15.4, 7.7, 4.1$ Hz, 1 H,
 $\text{CH}=\text{CHCH}_2$), 5.22-5.16 (m, 1 H, CO_2CH), 3.73 (dd, $J = 10.7,$
 5.7 Hz, 1 H, CH_2OTPS), 3.69 (dd, $J = 10.7, 4.9$ Hz, 1 H,
 CH_2OTPS), 3.14 (q, $J = 6.9$ Hz, 1 H, $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 3.11 (d,
 $J = 9.7$ Hz, 1 H, $\text{CHOH}(\text{CHCH}_3)$), 2.95 (bs, 1 H, $\text{CHOH}(\text{CHCH}_3)$),
 2.44-2.39 (m, 1 H), 2.30-2.23 (m, 1 H), 2.16-2.11 (m, 1
 H), 1.99-1.92 (m, 1 H), 1.44-1.38 (m, 2 H), 1.33 (s, 3 H,
 $\text{C}(\text{CH}_3)_2$), 1.23-1.05 (m, 3 H), 1.22 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.04
 (s, 9 H, $\text{SiC}(\text{CH}_3)_3(\text{C}_6\text{H}_5)_2$), 1.02 (d, $J = 6.9$ Hz, 3 H,
 $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 0.96 (d, $J = 6.5$ Hz, 3 H, CH_3CHCH_2); ^{13}C NMR
 (125.7 MHz, CDCl_3) δ 216.6, 164.8, 150.0, 135.5, 135.4,
 133.2, 133.2, 132.9, 129.6, 129.6, 127.6, 127.6, 126.3,
 122.5, 73.8, 73.3, 65.6, 52.0, 41.1, 36.0, 34.6, 33.6,
 32.4, 26.9, 25.7, 22.8, 22.8, 19.4, 16.2, 10.5; HRMS
 (FAB), calcd for $\text{C}_{36}\text{H}_{50}\text{O}_5\text{CsSi}$ ($M + \text{Cs}^+$) 723.2482, found
 723.2508.

Synthesis of Hydroxy Acids 33 and 34 as
 illustrated in Figure 6. Aldol Condensation of Acid
 21 with Aldehyde 7. A solution of keto acid 21 (752 mg,
 4.42 mmol, 1.0 equiv) in THF (22 mL) was added dropwise at
 -78 °C to a freshly prepared solution of LDA [formed by
 addition of $n\text{-BuLi}$ (6.49 mL, 1.6 M solution in hexanes,
 10.4 mmol, 2.35 equiv) to a solution of diisopropylamine
 (1.43 mL, 10.2 mmol, 2.3 equiv) in THF (44 mL) at -10 °C
 and stirring for 30 min]. After stirring for 15 min the

reaction mixture was allowed to warm to -30 °C and stirred at that temperature for 1.5 h. The reaction mixture was cooled back to -78 °C and a solution of aldehyde 7 (0.891 g, 7.07 mmol, 1.6 equiv) in THF (22 mL) was added via cannula. The resulting mixture was stirred for 15 min at -78 °C, then warmed to -40 °C and stirred for 1 h, cooled to -78 °C and quenched by slow addition of saturated aqueous NH₄Cl (10 mL) solution. The reaction mixture was warmed to 0 °C, and acetic acid (1.26 mL, 22.1 mmol, 5.0 equiv) was added, followed by warming to 25 °C. Extractions with EtOAc (6 x 15 mL), filtration through a short plug of silica gel and concentration afforded, in high yield, a mixture of aldol products 33 and 34 along with unreacted starting acid 21 in a 35:50:15 ratio (1H NMR). This crude material was used without further purification. 1H NMR (500 MHz, CDCl₃; only signals for 33 and 34 are reported) δ 7.16 (d, J = 16.0 Hz, 1 H, CH=CHCOOH), 5.95 (d, J = 16.0 Hz, 1 H, CH=CHCOOH), 5.86-5.73 (m, 1 H, CH₂CH=CH₂), 5.02-4.91 (m, 2 H, CH₂CH=CH₂), 3.46-3.32 (m, 1 H, CHOH(CH₂CH₃)), 3.17-3.11 (m, 1 H, CH₂CH(C=O)), 2.09-1.98 (m, 2 H, CH₂CH=CH₂), 1.72-1.24 (m, 9 H), 1.14-1.02 (m, 5 H), 0.95-0.81 (m, 3 H); HRMS (FAB), calcd for C₁₇H₂₉O₄ (M + H⁺) 297.2066, found 297.2074.

Synthesis of Esters 35 and 36 as illustrated in Figure 6. EDC Coupling of Alcohol 6 with Keto Acids 33 and 34. By analogy to the procedure described above for the synthesis of ester 22a, a solution of keto acids 33 and 34 (1.034 g crude), 4-dimethylaminopyridine (4-DMAP,

43 mg, 0.35 mmol), and alcohol 6 (1.1 g, 5.24 mmol; synthesized *vide infra* as compound 91; eg. alcohol 6 as shown in figure 6 is the same compound as compound 91 as shown in figure 12) in Methylene chloride (4 mL) was treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 1.00 g, 5.24 mmol) to provide, after column chromatography (silica gel, 20% EtOAc in hexanes), ester 35 (0.567 g, 29% from keto acid 21) and ester 36 (0.863 g, 44% from keto acid 21). 35: R_f = 0.27 (silica gel, 20% EtOAc in hexanes); [α]_D²² -7.3 (c 2.90, CHCl₃); IR (film) ν_{max} 3510, 2973, 2932, 1719, 1703, 1641, 1459, 1293, 1179, 985 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.03 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.95 (s, 1 H, ArH), 6.53 (s, 1 H, ArCH=CCH₃), 5.95 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.80-5.69 (m, 2 H, 2 x CH₂CH=CH₂), 5.39 (t, J = 6.5 Hz, 1 H, CO₂CH), 5.10 (d, J = 17.5 Hz, 1 H, CH₂CH=CH₂), 5.05 (d, J = 10.5 Hz, 1 H, CH₂CH=CH₂), 4.97 (d, J = 17.0 Hz, 1 H, CH₂CH=CH₂), 4.93 (d, J = 10.0 Hz, 1 H, CH₂CH=CH₂), 3.43 (dd, J = 6.5, 4.0 Hz, 1 H, CHOH(CHCH₃)), 3.11 (qd, J = 7.0, 4.0 Hz, 1 H, CH₃CH(C=O)), 2.76 (bs, 1 H, CHOH(CHCH₃)), 2.69 (s, 3 H, CH₃Ar), 2.57-2.47 (m, 2 H, CH₂CH=CH₂), 2.08 (d, J = 1.0 Hz, 3 H, ArCH=CCH₃), 2.07-1.93 (m, 2 H, CH₂CH=CH₂), 1.47-1.28 (m, 4 H), 1.30 (s, 3 H, C(CH₃)₂), 1.28 (s, 3 H, C(CH₃)₂), 1.05 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.05-0.98 (m, 1 H), 0.91 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 216.3, 165.0, 164.7, 152.2, 150.5, 138.6, 136.9, 133.2, 121.4, 120.8, 117.8, 116.4, 114.6, 78.4, 75.0, 51.5, 42.6, 37.5, 35.3, 33.7, 32.5, 25.9, 23.2, 23.2, 19.1, 14.8.

12.2; HRMS (FAB), calcd for $C_{28}H_{42}NO_4S$ ($M + H^+$) 488.2835, found 488.2843. 36: R_f = 0.34 (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{25}$ -9.2 (c 1.00, $CHCl_3$); IR (film) ν_{max} 3519, 2930, 1716, 1641, 1457, 1293, 1179, 986 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 16.0 Hz, 1 H, $CH=CHCOO$), 6.95 (s, 1 H, ArH), 6.54 (s, 1 H, $ArCH=CCH_3$), 5.96 (d, J = 15.5 Hz, 1 H, $CH=CHCOO$), 5.84-5.69 (m, 2 H, 2 x $CH_2CH=CH_2$), 5.40 (t, J = 6.5 Hz, 1 H, CO_2CH), 5.10 (d, J = 17.0 Hz, 1 H, $CH_2CH=CH_2$), 5.05 (d, J = 10.5 Hz, 1 H, $CH_2CH=CH_2$), 4.98 (d, J = 17.5 Hz, 1 H, $CH_2CH=CH_2$), 4.92 (d, J = 9.0 Hz, 1 H, $CH_2CH=CH_2$), 3.30 (dd, J = 8.5, 1.5 Hz, 1 H, $CHOH(CHCH_3)$), 3.13 (qd, J = 7.0, 2.0 Hz, 1 H, $CH_3CH(C=O)$), 2.70 (s, 3 H, CH_3Ar), 2.57-2.49 (m, 2 H, $CH_2CH=CH_2$), 2.09 (s, 3 H, $ArCH=CCH_3$), 2.09-1.96 (m, 2 H, $CH_2CH=CH_2$), 1.74-1.68 (m, 1 H), 1.52-1.43 (m, 2 H), 1.32 (s, 3 H, $C(CH_3)_2$), 1.30 (s, 3 H, $C(CH_3)_2$), 1.30-1.01 (m, 2 H), 1.02 (d, J = 7.0 Hz, 3 H, $CH_3CH(C=O)$), 0.79 (d, J = 6.5 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 217.3, 165.1, 164.7, 152.4, 150.4, 139.0, 136.8, 133.2, 121.6, 121.0, 117.8, 116.4, 114.3, 78.5, 74.9, 51.5, 41.5, 37.5, 35.4, 34.1, 32.1, 26.0, 23.2, 23.0, 19.2, 15.5, 14.7, 10.2; HRMS (FAB), calcd for $C_{28}H_{44}CsNO_4S$ ($M + Cs^+$) 620.1811, found 620.1838.

Synthesis of Hydroxy Lactone 37 as illustrated in Figure 6. Olefin Metathesis of Diene 35. A solution of diene 35 (58 mg, 0.12 mmol) in Methylene chloride (129 mL, 0.001 M) was treated with bis(tricyclohexylphosphine)ethylidene ruthenium

dichloride ((RuCl₂(=CHPh)(PCy₃)₂, 10 mg, 0.0012 mmol, 0.1 equiv; Aldrich), in accordance with the procedure described for the synthesis of hydroxy lactone 25, to furnish, after column chromatography (silica gel, 15% EtOAc in hexanes) hydroxy lactone 37 (48 mg, 86%). R_f = 0.63 (silica gel, 33% EtOAc in hexanes); [α]_D²⁵ -14.8 (c 1.90, CHCl₃); IR (film) ν_{max} 3510, 2931, 1709, 1646, 1458, 1295, 1178, 976, 732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.15 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.96 (s, 1 H, ArH), 6.58 (s, 1 H, ArCH=CCH₃), 5.95 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.56 (dd, J = 9.5, 3.0 Hz, 1 H, CO₂CH), 5.36 (ddd, J = 15.5, 7.3, 3.5 Hz, 1 H, CH=CHCH₂), 5.35 (ddd, J = 15.5, 7.3, 3.5 Hz, 1 H, CH=CHCH₂), 3.33 (d, J = 9.0 Hz, 1 H, CHOH(CHCH₃)), 3.16 (q, J = 7.0 Hz, 1 H, CH₃CH(C=O)), 2.88 (bs, 1 H, CHOH(CHCH₃)), 2.71 (s, 3 H, CH₃Ar), 2.56-2.42 (m, 2 H, CH=CHCH₂), 2.18-2.06 (m, 1 H, CH=CHCH₂), 2.10 (s, 3 H, ArCH=CCH₃), 1.99-1.90 (m, 1 H, CH=CHCH₂), 1.52-1.20 (m, 3 H), 1.31 (s, 3 H, C(CH₃)₂), 1.28 (s, 3 H, C(CH₃)₂), 1.17-0.90 (m, 2 H), 1.02 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 0.97 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 217.8, 165.1, 164.8, 152.1, 151.5, 138.3, 133.4, 125.8, 121.5, 119.3, 116.0, 76.8, 74.9, 50.8, 43.7, 36.7, 35.5, 32.5, 31.8, 25.4, 25.2, 23.9, 19.0, 15.8, 15.5, 9.7; HRMS (FAB), calcd for C₂₆H₃₇NO₄S (M + Cs⁺) 592.1498, found 592.1516.

Synthesis of Hydroxy Lactone 38 as illustrated in Figure 6. Olefin Metathesis of Diene 36. A solution of diene 36 (167 mg, 0.34 mmol) in Methylene chloride (340

mL, 0.001 M) was treated with

bis(tricyclohexylphosphine)benzylidene ruthenium

dichloride ((RuCl₂(=CHPh)(PCy₃)₂, 28 mg, 0.034 mmol, 0.1

equiv; Aldrich), in accordance with the procedure

described for the synthesis of hydroxy lactone 25, to

furnish, after column chromatography (silica gel, 20%

EtOAc in hexanes) hydroxy lactone 38 (103 mg, 66%). R_f =

0.38 (silica gel, 30% EtOAc in hexanes); [α]_D²⁵ +70.4 (c

1.60, CHCl₃); IR (film) ν_{max} 2933, 1703, 1640, 1292, 1179,

982 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.99 (d, J = 16.0 Hz,

1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 6.55 (s, 1 H,

ArCH=CCH₃), 6.02 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.51

(dd, J = 8.0, 2.5 Hz, 1 H, CO₂CH), 5.47 (ddd, J = 15.0,

7.5, 7.5 Hz, 1 H, CH=CHCH₂), 5.38 (ddd, J = 15.0, 7.5, 7.5

Hz, 1 H, CH=CHCH₂), 3.60 (d, J = 6.8 Hz, 1 H,

CHOH(CHCH₃)), 3.14 (dq, J = 7.0, 7.0 Hz, 1 H, CH₃CH(C=O)),

2.70 (s, 3 H, CH₃Ar), 2.48-2.37 (m, 2 H, CH=CHCH₂), 2.21-

2.12 (m, 1 H, CH=CHCH₂), 2.08 (s, 3 H, ArCH=CCH₃), 1.98-

1.90 (m, 1 H, CH=CHCH₂), 1.62-1.52 (m, 1 H), 1.41-1.32 (m,

2H), 1.36 (s, 3 H, C(CH₃)₂), 1.21 (s, 3 H, C(CH₃)₂), 1.17-

1.07 (m, 1H), 1.14 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 0.98-

0.87 (m, 1H), 0.97 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); ¹³C NMR

(125.7 MHz, CDCl₃) δ 215.5, 165.0, 164.6, 152.2, 150.9,

137.4, 133.6, 126.0, 121.9, 119.4, 115.6, 76.6, 76.2,

51.6, 44.1, 37.9, 36.2, 33.3, 29.6, 27.1, 24.0, 23.0,

18.9, 17.0, 15.9, 15.4; HRMS (FAB), calcd for C₂₆H₃₈NO₄S

(M + H⁺) 460.2522, found 460.2534.

Synthesis of Epothilones 39, 40 and 41 as

illustrated in Figure 6. Epoxidation of trans-Hydroxy Lactone 37. Procedure A: A solution of trans-hydroxy lactone 37 (20 mg, 0.06 mmol) in CHCl_3 (1 mL, 0.06 M) was treated with meta-chloroperoxybenzoic acid (mCPBA, 57-86 %, 15 mg, 0.05-0.07 mol, 0.9-1.2 equiv) at -20°C , and the reaction mixture was allowed to warm up to 0°C . After 12 h, disappearance of starting material was detected by TLC, and the reaction mixture was then washed with saturated aqueous NaHCO_3 solution (2 mL) and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic layer was dried (MgSO_4), filtered and concentrated. Purification by preparative thin layer chromatography (250 mm silica gel plate, 30% EtOAc in hexanes) furnished epothilones 39 (or 40) (12 mg, 40%), 40 (or 39) (7.5 mg, 25%) and 41 (5.4 mg, 18%). Procedure B: To a solution of trans-hydroxy lactone 37 (32 mg, 0.07 mmol) in acetonitrile (1.0 mL) was added a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA , 0.5 mL) and the reaction mixture was cooled to 0°C . Excess of 1,1,1-trifluoroacetone (0.2 mL) was added, followed by a portionwise addition of Oxone® (200 mg, 0.35 mmol, 5.0 equiv) and NaHCO_3 (50 mg, 0.56 mmol, 8.0 equiv) with stirring, until the disappearance of starting material was detected by TLC. The reaction mixture was then treated with excess dimethyl sulfide (150 mL) and water (1.0 mL) and then extracted with EtOAc (4 x 2 mL). The combined organic layer was dried (MgSO_4), filtered, and concentrated. Purification by preparative thin layer chromatography (250 mm silica gel plate, 70%

EtOAc in hexanes) provided a mixture of diastereomeric epoxides, epoxide 39 (or 40) (15 mg, 45%) and a-isomeric epoxide 40 (or 39) (9.2 mg, 28%). 39 (or 40): $R_f = 0.23$ (silica gel, 33% EtOAc in hexanes); $[\alpha]_{22D} -23.7$ (c 0.30, CHCl₃); IR (film) ν_{max} 3500, 2970, 2930, 2859, 1714, 1696, 1651, 1643, 1634, 1293, 1176, 991 cm^{-1} ; ¹H NMR (600 MHz, CDCl₃) δ 7.18 (d, $J = 16.0$ Hz, 1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 6.56 (s, 1 H, ArCH=CCH₃), 5.94 (d, $J = 16.0$ Hz, 1 H, CH=CHCOO), 5.71 (d, $J = 11.1$ Hz, 1 H, CO₂CH), 3.52 (d, $J = 6.0$ Hz, 1 H, CHOH(CHCH₃)), 3.07 (q, $J = 6.9$ Hz, 1 H, CH₃CH(C=O)), 2.76 (d, $J = 8.0$ Hz, 1 H), 2.70 (s, 3 H, CH₃Ar), 2.61 (bs, 2 H), 2.29 (d, $J = 14.5$ Hz, 1 H), 2.09 (s, 3 H, ArCH=CCH₃), 1.82-1.76 (m, 1 H), 1.75-1.68 (m, 1 H), 1.60-0.98 (m, 6 H), 1.35 (s, 3 H, C(CH₃)₂), 1.29 (s, 3 H, C(CH₃)₂), 1.11 (d, $J = 6.9$ Hz, 3 H, CH₃CH(C=O)), 1.01 (d, $J = 6.7$ Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 216.4, 165.1, 164.7, 152.0, 151.9, 136.7, 121.3, 120.5, 116.6, 76.3, 72.3, 59.3, 56.6, 51.1, 45.2, 36.7, 36.7, 33.3, 32.2, 25.3, 23.5, 22.4, 19.4, 15.5, 15.1, 10.9; HRMS (FAB), calcd for C₂₆H₃₇NO₅S (M + H⁺) 608.1447, found 608.1469; 40 (or 39): $R_f = 0.26$ (silica gel, 33% EtOAc in hexanes); $[\alpha]_{22D} -20.0$ (c 0.25, CHCl₃); IR (film) ν_{max} 3517, 2927, 2856, 1715, 1698, 1644, 1293, 1176, 989 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 7.26 (d, $J = 16.0$ Hz, 1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 6.56 (s, 1 H, ArCH=CCH₃), 5.98 (d, $J = 16.0$ Hz, 1 H, CH=CHCOO), 5.50 (d, $J = 6.5$ Hz, 1 H, CO₂CH), 3.47 (d, $J = 8.0$ Hz, 1 H, CHOH(CHCH₃)), 3.19 (q, $J = 7.0$ Hz, 1 H, CH₃CH(C=O)), 2.78 (t, $J = 6.5$ Hz, 2 H), 2.71 (s, 3 H, CH₃Ar), 2.32-2.26 (m, 1 H), 2.11 (s, 3

H, ArCH=CCH₃), 1.91-1.86 (m, 1 H), 1.76-1.17 (m, 7 H),
 1.36 (s, 3 H, C(CH₃)₂), 1.30 (s, 3 H, (C(CH₃)₂), 1.08 (d,
 J = 7.0 Hz, 3 H, CH₃CH(C=O)), 0.98 (d, J = 6.5 Hz, 3 H,
 CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 216.9, 165.0,
 164.6, 152.0, 151.4, 136.6, 121.7, 119.6, 116.3, 76.1,
 73.6, 57.3, 54.1, 51.2, 44.1, 35.3, 35.0, 32.8, 30.8,
 24.3, 23.6, 21.9, 19.3, 16.1, 15.5, 10.7; HRMS (FAB),
 calcd for C₂₆H₃₈NO₅S (M + Cs⁺) 608.1447, found 608.1469.
 41: R_f = 0.43 (silica gel, 33% EtOAc in hexanes); [α]_D²²
 -14.0 (c 0.10, CHCl₃); IR (film) ν_{max} 3482, 2925, 1722,
 1642, 1176 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.14 (d, J =
 16.0 Hz, 1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 5.92 (d, J =
 16.0 Hz, 1 H, CH=CHCOO), 5.35-5.33 (m, 2 H, CH=CHCH₂),
 5.13 (dd, J = 10.5, 3.0 Hz, 1 H, CO₂CH), 4.20 (s, 1 H,
 ArCH-O(epoxide)CCH₃), 3.30 (d, J = 9.0 Hz, 1 H,
 CHOH(CHCH₃)), 3.13 (q, J = 7.5 Hz, 1 H, CH₃CH(C=O)), 2.76
 (d, J = 2.0 Hz, 1 H), 2.72 (s, 3 H, CH₃Ar), 2.58 (dd, J =
 14.1, 2.4 Hz, 1 H), 2.46-2.40 (m, 1 H), 2.22-2.16 (m, 1
 H), 2.02-1.87 (m, 2 H) 1.68- 0.82 (m, 3 H), 1.31 (s, 3 H,
 C(CH₃)₂), 1.28 (s, 3 H, C(CH₃)₂), 1.25 (s, 3 H, ArCH-
 O(epoxide)CCH₃), 1.01 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)),
 0.97 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz,
 CDCl₃) δ 217.5, 166.3, 165.1, 152.1, 150.9, 133.8, 125.4,
 121.0, 115.5, 75.1, 74.2, 59.5, 51.0, 44.0, 35.7, 34.1,
 32.7, 32.0, 29.8, 25.6, 25.5, 24.1, 19.3, 16.0, 13.0, 9.8;
 HRMS (FAB), calcd for C₂₆H₃₇NO₅S (M + Cs⁺) 608.1447,
 found 608.1423.

Synthesis of Epothilones 42, 43 and 44 as

illustrated in Figure 6. Epoxidation of trans-Hydroxy Lactone 38. Procedure A: A solution of trans-hydroxy lactone 38 (32 mg, 0.07 mmol) in CHCl_3 (1.4 mL) was reacted with meta-chloroperbenzoic acid (mCPBA, 57-86%, 17.8 mg, 0.06-0.09 mmol, 0.9-1.3 equiv), according to procedure A described for the epoxidation of 37, resulting in the isolation of epoxides 42 (or 43) (7.3 mg, 22%), 43 (or 42) (3.7 mg, 11%), and 44 (2.2 mg, 7%) (stereochemistry unassigned for all compounds), along with unreacted starting material (3.5 mg, 11%), after two consecutive preparative thin layer chromatographic purifications (250 mm silica gel plate, ether). Procedure B: As described in procedure B for the epoxidation of trans-hydroxy lactone 37, cis-hydroxy lactone 38 (24 mg, 0.05 mmol) in MeCN (800 mL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA , 380 mL), 1,1,1-trifluoroacetone (150 mL), Oxone® (144 mg, 0.25 mmol, 5.0 equiv) and NaHCO_3 (36 mg, 0.40 mmol, 8.0 equiv), to yield, after purification by preparative thin layer chromatography (250 mm silica gel plate, ether), epoxides 42 (or 43) (15 mg, 60%), 43 (or 42) (3.8 mg, 15%). 42 (or 43): $R_f = 0.60$ (silica gel, ether); $[\alpha]_{22D} +78.5$ (c 0.94, CHCl_3); IR (film) ν_{max} 3500, 2929, 1714, 1644, 1462, 1293, 1179, 982 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.98 (s, 1 H, ArH), 6.89 (d, $J = 16.0$ Hz, 1 H, $\text{CH}=\text{CHCOO}$), 6.58 (s, 1 H, ArCH=CCH₃), 6.06 (d, $J = 16.0$ Hz, 1 H, $\text{CH}=\text{CHCOO}$), 5.69 (d, $J = 11.0$ Hz, 1 H, CO_2CH), 3.80-3.73 (m, 1 H, $\text{CHOH}(\text{CHCH}_3)$), 3.11 (dq, $J = 7.0, 7.0$ Hz, 1 H, $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 2.82-2.74 (d,

2 H), 2.71 (s, 3 H, CH₃Ar), 2.43 (d, J = 14.5 Hz, 1 H),
 2.11 (s, 3 H, ArCH=CCH₃), 1.93-1.85 (m, 1 H), 1.60-0.98
 (m, 7 H), 1.46 (s, 3 H, C(CH₃)₂), 1.24 (s, 3 H, C(CH₃)₂),
 1.14 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.01 (d, J = 7.0
 5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 212.7,
 165.0, 164.7, 152.0, 151.7, 137.0, 121.1, 120.6, 116.7,
 76.2, 75.7, 58.7, 57.7, 52.2, 44.4, 37.3, 36.1, 33.5,
 30.0, 24.2, 23.0, 22.1, 19.3, 18.1, 14.9, 14.5; HRMS
 (FAB), calcd for C₂₆H₃₇NO₅S (M + H⁺) 476.2471, found
 10 476.2485. 43 (or 42): R_f = 0.64 (silica gel, ether);
 [α]_D²⁵ +38.0 (c 0.20, CHCl₃); IR (film) ν_{max} 3479, 2926,
 2855, 1721, 1702, 1643, 1455, 1174 cm⁻¹; ¹H NMR (500 MHz,
 CDCl₃) δ 7.08 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 7.01 (s, 1
 H, ArH), 6.63 (s, 1 H, ArCH=CCH₃), 6.05 (d, J = 16.0 Hz, 1
 15 H, CH=CHCOO), 5.47 (dd, J = 7.6, 2.6 Hz, 1 H, CO₂CH), 3.65
 (dd, J = 6.5, 3.5 Hz, 1 H, CHOH(CHCH₃)), 3.19 (dq, J =
 6.8, 6.8 Hz, 1 H, CH₃CH(C=O)), 2.85-2.80 (m, 1 H), 2.78-
 2.72 (m, 1 H), 2.73 (s, 3 H, CH₃Ar), 2.52 (ddd, J = 15.0,
 8.5, 4.0 Hz, 1 H), 2.10 (s, 3 H, ArCH=CCH₃), 1.73 (ddd, J
 20 = 15.0, 7.5, 3.5 Hz, 1 H), 1.65-0.80 (m, 7 H), 1.43 (s, 3
 H, C(CH₃)₂), 1.26 (s, 3 H, C(CH₃)₂), 1.15 (d, J = 6.8 Hz,
 3 H, CH₃CH(C=O)), 0.99 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); ¹³C
 NMR (150.9 MHz, CDCl₃) δ 215.1, 165.5, 164.7, 152.1,
 152.0, 130.9, 128.8, 120.9, 115.9, 75.7, 75.2, 57.6, 55.6,
 25 51.7, 44.3, 37.5, 34.4, 32.3, 31.1, 23.9, 23.3, 22.8,
 18.8, 17.2, 15.8, 14.6; HRMS (FAB), calcd for C₂₆H₃₇NO₅S
 (M + H⁺) 476.2471, found 476.2489. 44: R_f = 0.60 (silica
 gel, ether); [α]_D²⁵ +23.3 (c 0.06, CHCl₃); IR (film) ν_{max}
 3443, 2924, 1731, 1462, 1260 cm⁻¹; ¹H NMR (500 MHz, CDCl₃)

d 6.97 (s, 1 H, ArH), 6.84 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.04 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.51-5.43 (m, 1H, CH=CHCH₂), 5.42-5.35 (m, 1H, CH=CHCH₂), 5.05 (dd, J = 10.0, 2.5 Hz, 1 H, CO₂CH), 4.18 (s, 1H, ArCH-O(epoxide)CCH₃), 3.60-3.57 (m, 1 H, CHOH(CHCH₃)), 3.06 (dq, J = 7.0, 7.0 Hz, 1 H, CH₃CH(C=O)), 2.72 (s, 3 H, CH₃Ar), 2.56-2.50 (m, 1 H), 2.40-2.32 (m, 1 H), 2.30-2.22 (m, 1 H), 2.14-1.96 (m, 2 H), 1.60-0.98 (m, 4 H), 1.38 (s, 3H, ArCH-O(epoxide)CCH₃), 1.30 (s, 3 H, C(CH₃)₂), 1.22 (s, 3 H, C(CH₃)₂), 1.14 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 0.95 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); HRMS (FAB), calcd for C₂₆H₃₈NO₅S (M + H⁺) 476.2471, found 476.2492.

Synthesis of Hydroxy Keto Acids 45 and 46 as illustrated in Figure 7. Aldol Condensation of Keto Acid 8 and Aldehyde 7. In accordance with the procedure described for the synthesis of keto acids 33 and 34, keto acid 8 (0.896 g, 2.97 mmol, 1.0 equiv) in THF (10 mL) was treated with lithium diisopropylamide [LDA; freshly prepared from n-BuLi (4.36 mL, 1.6 M solution in hexanes, 7.41 mmol, 2.5 equiv) and diisopropylamine (960 mL, 6.83 mmol, 2.3 equiv) in THF (30 mL)] and aldehyde 7 (0.68 g, 5.3 mmol, 1.8 equiv) in THF (30 mL) to afford a mixture of aldol products 45 and 46 in high yield and in a ca 3:2 ratio (1H NMR), along with unreacted keto acid 8 (5%). R_f = 0.20 (silica gel, 50% EtOAc in hexanes); 1H NMR (500 MHz, CDCl₃; only signals for 45 and 46 are reported) d 5.88-5.73 (m, 1 H, CH₂CH=CH₂), 5.04-4.92 (m, 2 H, CH₂CH=CH₂), 4.51-4.47 (m, 0.4 H, CHOTBS), 4.44-4.40 (m,

0.6 H, (CH₃)₂CCH(OTBS)), 3.42 (d, J = 8.0 Hz, 0.4 H, CHOH(CHCH₃)), 3.32 (d, J = 9.0 Hz, 0.6 H, CHOH(CHCH₃)), 3.30-3.20 (m, 1 H, CH₃CH(C=O)), 2.51-2.45 (m, 1 H, CH₂COOH), 2.38 (dd, J = 16.5, 6.5 Hz, 0.4 H, CH₂COOH), 2.35 (dd, J = 16.5, 6.5 Hz, 0.6 H, CH₂COOH), 2.11-1.98 (m, 2 H), 1.80-1.21 (m, 5 H), 1.20 (s, 1.8 H, C(CH₃)₂), 1.19 (s, 1.2 H, C(CH₃)₂), 1.16 (s, 1.8 H, C(CH₃)₂), 1.14 (s, 1.2 H, C(CH₃)₂), 1.06 (d, J = 6.5 Hz, 1.2 H), 1.05 (d, J = 6.5 Hz, 1.8 H), 1.00 (d, J = 6.5 Hz, 1.2 H), 0.89 (s, 5.4 H, SiC(CH₃)₃(CH₃)₂), 0.87 (s, 3.6 H, SiC(CH₃)₃(CH₃)₂), 0.85 (d, J = 7.0 Hz, 1.8 H), 0.11 (s, 1.8 H, SiC(CH₃)₃(CH₃)₂), 0.09 (s, 1.2 H, SiC(CH₃)₃(CH₃)₂), 0.08 (s, 1.2 H, SiC(CH₃)₃(CH₃)₂), 0.07 (s, 1.8 H, SiC(CH₃)₃(CH₃)₂); HRMS (FAB), calcd for C₂₃H₄₄NaO₅Si (M + Na⁺) 451.2856, found 451.2867.

Synthesis of Hydroxy Esters 4 and 47 as illustrated in Figure 7. EDC Coupling of Carboxylic Acids 45 and 46 and Alcohol 6. The crude mixture of keto acids 45 and 46 (1.30 g), 4-(dimethylamino)pyridine (4-DMAP, 0.037 g, 0.3 mmol), and alcohol 6 (1.90 g, 9.0 mmol; synthesized *vide infra* as compound 91; eg. alcohol 6 as shown in figure 6 is the same compound as compound 91 as shown in figure 12) in Methylene chloride (5 mL) was treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 0.7 g, 3.6 mmol), according to the procedure described for the synthesis of keto ester 22a, producing pure hydroxy esters 4 (0.940 g, 52% from keto acid 8) and 47 (0.569 g, 31% from keto acid 8) after flash column chromatography

(silica gel, 18% EtOAc in hexanes).. 4: R_f = 0.30 (silica gel, 18% EtOAc in hexanes); [α]_D²² -53.4 (c 1.00, MeOH); IR (film) ν_{max} 3508, 2932, 1737, 1690, 1650, 1178, 1088, 835 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃): δ 6.93 (s, 1 H, ArH), 6.47 (s, 1 H, ArCH=CCH₃), 5.81-5.73 (m, 1 H, CH₂CH=CH₂), 5.73-5.65 (m, 1 H, CH₂CH=CH₂), 5.27 (dd, J = 7.0, 6.5 Hz, 1 H, CO₂CH), 5.09 (d, J = 17.5 Hz, 1 H, CH₂CH=CH₂), 5.03 (d, J = 10.0 Hz, 1 H, CH₂CH=CH₂), 4.96 (d, J = 17.0 Hz, 1 H, CH₂CH=CH₂), 4.89 (d, J = 10.5 Hz, 1 H, CH₂CH=CH₂), 4.39 (dd, J = 6.0, 4.0 Hz, 1 H, (CH₃)₂CCH(OTBS)), 3.42 (bs, 1 H, CHOH(CHCH₃)), 3.28 (q, J = 7.0 Hz, 1 H, CH₃CH(C=O)), 3.24 (d, J = 9.5 Hz, 1 H, CHOH(CHCH₃)), 2.67 (s, 3 H, CH₃Ar), 2.54-2.43 (m, 2 H), 2.43 (dd, J = 10.0, 4.0 Hz, 1 H, CH₂COO), 2.31 (dd, J = 10.0, 6.0 Hz, 1 H, CH₂COO), 2.04 (s, 3 H, ArCH=CCH₃), 2.03-1.90 (m, 2 H, CH₂CH=CH₂), 1.75-1.65 (m, 1 H), 1.48-1.43 (m, 1 H), 1.43-1.36 (m, 1 H), 1.22-1.10 (m, 2 H), 1.17 (s, 3 H, C(CH₃)₂), 1.09 (s, 3 H, C(CH₃)₂), 1.01 (d, J = 6.5 Hz, 3 H, CH₃CH(C=O)), 0.86 (s, 9 H, SiC(CH₃)₃(CH₃)₂), 0.81 (d, J = 7.0 Hz, 3 H CH₃CHCH₂), 0.09 (s, 3 H, SiC(CH₃)₃(CH₃)₂), 0.04 (s, 3 H, SiC(CH₃)₃(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 221.8, 170.9, 164.6, 152.4, 139.0, 136.6, 133.2, 121.0, 117.8, 116.4, 114.1, 78.8, 74.5, 73.4, 53.9, 41.2, 40.1, 37.4, 35.4, 34.1, 32.3, 26.0, 25.9, 21.9, 19.9, 19.2, 18.1, 15.2, 14.6, 9.7, -4.3, -4.9; HRMS (FAB), calcd for C₃₄H₅₇CsNO₅SSi (M + Cs⁺) 752.2781, found 752.2760. 47: R_f = 0.20 (silica gel, 18% EtOAc in hexanes); [α]_D²² -27.3 (c 1.00, CHCl₃); IR (film) ν_{max} 3509, 2932, 2857, 1737, 1691, 1465, 1381, 1292, 1253, 1177, 1088, 984, 835 cm⁻¹;

1H NMR (500 MHz, CDCl₃) δ 6.95 (s, 1 H, ArH), 6.49 (s, 1
 H, ArCH=CCH₃), 5.83-5.69 (m, 2 H, 2 x CH₂CH=CH₂), 5.29
 (dd, J = 6.5, 6.5 Hz, 1 H, CO₂CH), 5.11 (d, J = 17.0 Hz, 1
 H, CH₂CH=CH₂), 5.05 (d, J = 10.0 Hz, 1 H, CH₂CH=CH₂), 5.01
 5 (d, J = 17.0 Hz, 1 H, CH₂CH=CH₂), 4.95 01 (d, J = 10.5 Hz,
 1 H, CH₂CH=CH₂), 4.50 (dd, J = 6.5, 4.0 Hz, 1 H,
 (CH₃)₂CCH(OTBS)), 3.42 (dd, J = 8.0, 1.5 Hz, 1 H,
 CHOH(CHCH₃)), 3.21 (qd, J = 7.0, 2.0 Hz, 1 H, CH₃CH(C=O)),
 2.70 (s, 3 H, CH₃Ar), 2.54-2.33 (m, 4 H), 2.11-1.98 (m, 2
 10 H), 2.07 (s, 3 H, ArCH=CCH₃), 1.53-0.98 (m, 5 H), 1.15 (s,
 3 H, C(CH₃)₂), 1.11 (s, 3 H, C(CH₃)₂), 1.01 (d, J = 7 Hz,
 3 H, CH₃CH(C=O)), 0.99 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂),
 0.86 (s, 9 H, SiC(CH₃)₃(CH₃)₂), 0.08 (s, 3 H,
 SiC(CH₃)₃(CH₃)₂), 0.07 08 (s, 3 H, SiC(CH₃)₃(CH₃)₂); ¹³C
 15 NMR (125.7 MHz, CDCl₃) δ 220.8, 170.9, 164.4, 152.2,
 138.6, 136.6, 133.1, 120.9, 117.8, 116.3, 114.5, 78.8,
 74.8, 72.5, 53.9, 41.3, 40.1, 37.4, 35.2, 33.7, 32.0,
 25.9, 25.8, 21.7, 19.6, 19.1, 18.1, 15.4, 14.5, 10.5,
 -4.4, -4.8; HRMS (FAB), calcd for C₃₄H₅₈NO₅SSi (M + H+)
 20 620.3805, found 620.3813.

Synthesis of Hydroxy Lactones 3 and 48 as
 illustrated in Figure 8. Cyclization of Diene 42 via
 Olefin Metathesis. A solution of diene 4 (0.186 g, 0.3
 25 mmol) in Methylene chloride (200 mL, 0.0015 M) was treated
 with bis(tricyclohexyl-phosphine)-benzylidene ruthenium
 dichloride (RuCl₂(=CHPh)(PCy₃)₂, 25 mg, 0.03 mol, 0.1
 equiv; Aldrich), for 20 h, in accordance with the
 procedure described for the synthesis of hydroxy lactone

25, producing hydroxy lactones 3 (83 mg, 46%) and 48 (70 mg, 39%) after flash chromatography (7 to 25% EtOAc in hexanes). 3: R_f = 0.18 (silica, 20% EtOAc in hexanes); $[\alpha]_{22D} -79.5$ (c = 1.00, $CHCl_3$); IR (film) ν_{max} 3422, 2930, 1739, 1688, 1255, 1180, 1090, 598 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1 H, ArH), 6.55 (s, 1 H, ArCH=CCH₃), 5.45 (ddd, J = 10.5, 10.5, 3.0 Hz, 1 H, CH=CHCH₂), 5.35 (ddd, J = 10.5, 10.5, 5.5 Hz, 1 H, CH=CHCH₂), 5.03 (d, J = 10.0 Hz, 1 H, CO₂CH), 4.06 (t, J = 6.0 Hz, 1 H, (CH₃)₂CCH(OTBS)), 3.94 (bs, 1 H, CHOH(CHCH₃)), 3.05 (qd, J = 6.5, 3.5 Hz, 1 H, CH₃CH(C=O)), 3.00 (bs, 1 H, CHOH(CHCH₃)), 2.80 (d, J = 6.0 Hz, 2 H, CH₂COO), 2.78-2.69 (m, 1 H), 2.70 (s, 3 H, CH₃Ar), 2.40-2.30 (m, 1 H), 2.10 (s, 3 H, ArCH=CCH₃), 2.12-2.03 (m, 1 H), 2.00-1.93 (m, 1 H), 1.80-1.74 (m, 1 H), 1.70-1.58 (m, 1 H), 1.50-1.43 (m, 1 H), 1.30-1.15 (m, 2 H), 1.17 (s, 6 H, C(CH₃)₂), 1.14 (d, 3 H, J = 5.0 Hz, CH₃CH(C=O)), 1.02 (d, 3 H, J = 5.0 Hz, CH₃CHCH₂), 0.82 (s, 9 H, SiC(CH₃)₃(CH₃)₂), 0.12 (s, 3 H, SiC(CH₃)₃(CH₃)₂), -0.05 (s, 3 H, SiC(CH₃)₃(CH₃)₂); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.7, 170.7, 164.4, 152.2, 138.1, 134.5, 124.0, 119.5, 116.0, 79.0, 76.3, 73.2, 53.6, 43.1, 39.1, 38.9, 33.7, 32.0, 28.5, 28.0, 26.3, 24.9, 23.0, 19.3, 18.7, 16.6, 15.4, 14.3, -3.4, -5.3; HRMS (FAB), calcd for C₃₂H₅₃CsNO₅SSi ($M + Cs^+$) 724.2468, found 724.2466. 48: R_f = 0.40 (silica, 20% EtOAc in hexanes); $[\alpha]_{22D} -71.5$ (c = 0.80, $CHCl_3$); IR (film) ν_{max} 3381, 2958, 2928, 1727, 1273, 1122, 1072 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 7.00 (s, 1 H, ArH), 6.62 (s, 1 H, ArCH=CCH₃), 5.36 (ddd, J = 15.0, 7.3, 7.3 Hz, 1 H, CH=CHCH₂), 5.27 (ddd, J

= 15.0, 7.3, 7.3 Hz, 1 H, CH=CHCH₂), 5.19 (dd, J = 6.5, 3.6 Hz, 1 H, CO₂CH), 4.43 (dd, J = 8.6, 2.7 Hz, 1 H, (CH₃)₂CCH(OTBS)), 3.87-3.83 (m, 1 H, CHOH(CHCH₃)), 3.33-3.25 (bs, 1 H, CHOH(CHCH₃)), 3.19 (qd, J = 6.9, 5.4 Hz, 1 H, CH₃CH(C=O)), 2.71 (s, 3 H, CH₃Ar), 2.72-2.67 (m, 1 H), 2.65 (dd, J = 15.4, 8.6 Hz, 1 H, CH₂COO), 2.59 (dd, J = 15.4, 2.7 Hz, 1 H, CH₂COO), 2.45-2.37 (m, 1 H), 2.20-2.12 (m, 1 H), 2.08 (s, 3 H, CH₃C=CH), 2.00-1.93 (m, 1 H), 1.65-1.44 (m, 4 H), 1.22 (d, 3 H, J = 6.9 Hz, CH₃CH(C=O)), 1.2-1.12 (m, 1 H), 1.15 (s, 3 H, C(CH₃)₂), 1.09 (s, 3 H, C(CH₃)₂), 1.03 (d, 3 H, J = 6.9 Hz, CH₃CHCH₂), 0.86 (s, 9 H, SiC(CH₃)₃(CH₃)₂), 0.08 (s, 3 H, SiC(CH₃)₃(CH₃)₂), 0.00 (s, 3 H, SiC(CH₃)₃(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 217.9, 169.9, 164.7, 152.1, 136.3, 134.5, 124.9, 119.4, 115.4, 77.4, 75.1, 74.1, 54.1, 43.9, 41.0, 38.5, 35.3, 33.0, 30.9, 27.0, 26.2, 23.8, 21.7, 19.1, 18.5, 17.0, 16.1, 14.8, -3.8, -4.2; HRMS (FAB), calcd for C₃₂H₅₃CsNO₅SSi (M + Cs⁺) 724.2468, found 724.2479.

Synthesis of cis-Dihydroxy Lactone 49 as illustrated in Figure 8. Desilylation of Compound 3. Silyl ether 3 (30 mg, 0.05 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-Methylene chloride (0.3 mL, 0.17 M) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h (completion of the reaction by TLC), and the solvents were evaporated under reduced pressure. The crude reaction mixture was purified by preparative thin layer chromatography (0.5 mm silica gel plate, 50% EtOAc in hexanes) to obtain-cis-

dihydroxy lactone 49 (22 mg, 90%). $R_F = 0.30$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_{22D} -80.2$ (c 1.36, $CHCl_3$); IR (thin film) ν_{max} 3453, 2929, 1733, 1686, 1506, 1464, 1250, 978 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1 H, ArH), 6.59 (s, 1 H, ArCH=C(CH₃)), 5.44 (ddd, $J = 10.5, 10.5, 4.5$ Hz, 1 H, CH=CHCH₂), 5.36 (ddd, $J = 10.5, 10.5, 5.0$ Hz, 1 H, CH=CHCH₂), 5.28 (d, $J = 9.4$ Hz, 1 H, CO₂CH), 4.23 (d, $J = 11.1$ Hz, 1 H, (CH₃)₂CCH(OH)), 3.72 (m, 1 H, CHOH(CHCH₃)), 3.43-3.37 (m, 1 H, OH), 3.14 (q, $J = 6.7$ Hz, 1 H, CH₃CH(C=O)), 3.05 (bs, 1 H, OH), 2.72-2.63 (m, 1 H), 2.69 (s, 3 H, CH₃Ar), 2.48 (dd, $J = 14.8, 11.3$ Hz, 1 H, CH₂COO), 2.33 (dd, $J = 14.8, 2.0$ Hz, 1H, CH₂COO), 2.30-2.13 (m, 2 H) 2.07 (s, 3 H, ArCH=CCH₃), 2.07-1.98 (m, 1 H), 1.80-1.60 (m, 2H), 1.32 (s, 3 H, C(CH₃)₂), 1.36-1.13 (m, 3H), 1.17 (d, $J = 6.8$ Hz, 3 H, CH₃CH(C=O)), 1.06 (s, 3 H, C(CH₃)₂), 0.99 (d, $J = 7.0$ Hz, 3 H, CH₃CHCH₂); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.6, 170.4, 165.0 151.9, 138.7, 133.4, 125.0, 119.4, 115.8, 78.4, 74.1, 72.3, 53.3, 41.7, 39.2, 38.5, 32.4, 31.7, 27.6, 27.4, 22.7, 19.0, 18.6, 15.9, 15.5, 13.5; HRMS (FAB), calcd for C₂₆H₃₉CsNO₅S (M + Cs+) 610.1603, found 610.1580.

Synthesis of trans-Dihydroxy Lactone 50 as illustrated in Figure 8. Desilylation of Compound 48. Silyl ether 48 (32 mg, 0.05 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)-Methylene chloride (0.3 mL, 0.17 M), according to the procedure described for cis-dihydroxy lactone 49, to yield, after preparative thin layer chromatography (0.5

mm silica gel plate, 50% EtOAc in hexanes), trans-dihydroxy ester 50 (24 mg, 92%). R_f = 0.15 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{25}$ -62.7 (c 1.65, CHCl_3); IR (film) ν_{max} 3428, 2932, 1730, 1692, 1468, 1253, 976 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.97 (s, 1 H, ArH), 6.56 (s, 1 H, ArCH=CCH₃), 5.49 (ddd, J = 15.0, 4.7, 4.7 Hz, 1 H, CH=CHCH₂), 5.38 (dd, J = 5.7, 5.7 Hz, 1 H, CO₂CH), 5.37 (ddd, J = 15.0, 6.5, 6.5 Hz, 1 H, CH=CHCH₂), 4.18 (d, J = 10.5 Hz, 1 H, (CH₃)₂CCH(OH)), 3.73 (m, 1 H, CHOH(CHCH₃)), 3.27-3.20 (m, 2 H, CH₃CH(C=O) and OH), 2.82 (bs, 1 H, OH), 2.70 (s, 3 H, CH₃Ar), 2.55 (dd, J = 15.5, 10.5 Hz, 1 H, CH₂COO), 2.48-2.43 (m, 3 H), 2.18-2.12 (m, 1 H), 2.07 (s, 3 H, ArCH=CCH₃), 1.98-1.91 (m, 1 H), 1.63-1.55 (m, 2 H), 1.46 (dddd, J = 12.5, 12.5, 4.0, 4.0 Hz, 1 H), 1.27' (s, 3 H, C(CH₃)₂), 1.19 (m, 2 H), 1.17 (d, J = 6.5 Hz, 3 H, CH₃CH(C=O)), 1.06 (s, 3 H, C(CH₃)₂), 0.97 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂); ^{13}C NMR (125.7 MHz, CDCl_3) δ 219.8, 170.4, 164.9, 151.9, 137.1, 134.2, 125.6, 119.6, 115.9, 77.5, 75.7, 72.2, 52.5, 43.5, 38.8, 37.6, 36.1, 32.3, 31.2, 26.9, 21.3, 21.1, 19.1, 17.0, 15.7, 14.3; HRMS (FAB), calcd for C₂₆H₄₀NO₅S (M + H⁺) 478.2627, found 478.2612.

Synthesis of Epothilones A (1) and 51-57 as illustrated in Figure 8. Epoxidation of cis-Dihydroxy Lactone 49. Procedure A: A solution of cis-dihydroxy lactone 49 (24 mg, 0.05 mmol) in CHCl_3 (4.0 mL) was reacted with meta-chloroperoxybenzoic acid (mCPBA, 57-86%, 13.0 mg, 0.04-0.06 mmol, 0.8-1.2 equiv), at -20 to 0 °C,

according to the procedure described for the epoxidation of 37, resulting in the isolation of epothilone A (1) (8.6 mg, 35%), its isomeric α -epoxide 51 (2.8 mg, 13%), and compounds 52 (or 53) (1.6 mg, 9%), 53 (or 52) (1.5 mg, 7%), 54 (or 55) (1.0 mg, 5%), and 55 (or 54) (1.0 mg, 5%) (stereochemistry unassigned for 52 and 53 and for 54 and 55), after two consecutive preparative thin layer chromatographic purifications (250 mm silica gel plate, 5% MeOH in Methylene chloride and 70% EtOAc in hexanes).

Procedure B: To a solution of cis-dihydroxy lactone 49 (15 mg, 0.03 mmol) in Methylene chloride (1.0 mL) at 0 °C was added dropwise a solution of dimethyldioxirane in acetone (ca 0.1 M, 0.3 mL, ca 1.0 equiv) until no starting lactone was detectable by TLC. The solution was then concentrated in vacuo and the crude product was subjected to two consecutive preparative thin layer chromatographic purifications (250 mm silica gel plate, 5% MeOH in Methylene chloride and 70% EtOAc in hexanes), to obtain pure epothilone A (1) (7.4 mg, 50%), its isomeric α -

epoxide 51 (2.3 mg, 15%), and epothilones 52 (or 53) (0.8 mg, 5%) and 53 (or 52) (0.8 mg, 5%) (stereochemistry unassigned for 52 and 53). Procedure C: As described in procedure B for the epoxidation of trans-hydroxy lactone 37, cis-dihydroxy lactone 49 (10.0 mg, 0.02 mmol) in MeCN (200 mL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA , 120 mL), excess 1,1,1-trifluoroacetone (100 mL), Oxone® (61 mg, 0.10 mmol, 5.0 equiv) and NaHCO_3 (14 mg, 0.16 mmol, 8.0 equiv), to yield, after purification by

preparative thin layer chromatography (250 mm silica gel plate, ether), a mixture of diastereomeric epoxides, epothilones A (1) (6.4 mg, 62%) and a-isomeric epoxide 51 (1.3 mg, 13%). Procedure D: A solution of cis-dihydroxy lactone 49 (18 mg, 0.037 mmol) in CHCl₃ (1.0 mL) was treated with meta-chloroperoxybenzoic acid (mCPBA, 57-86 %, 15 mg, 0.049-0.074 mmol, 1.3-2.0 equiv), according to the procedure described for the epoxidation of 37, furnishing compounds 1 (2.7 mg, 15%), 51 (1.8 mg, 10%), 52 (or 53) (1.8 mg, 10%), 53 (or 52) (1.4 mg, 8%), 54 (or 55) (1.4 mg, 8%), 55 (or 54) (1.26 mg, 7%), 56 (0.9 mg, 5%), and 57 (0.9 mg, 5%) (stereochemistry unassigned for 52-57), after two consecutive preparative thin layer chromatographic purifications (250 mm silica gel plate, 5% MeOH in Methylene chloride and 70% EtOAc in hexanes). Epothilone A (1): R_f = 0.23 (silica gel, 33% MeOH-Methylene chloride); HPLC (Watman EOC, C-18, 4 m, 108 x 4.6 mm column, solvent gradient: 0 & 20 min, 30 & 80% MeOH in H₂O) R_t = 14.8 min; [α]_D = -45.0 (c 0.02, MeOH); IR (film) ν_{max} 3476, 2974, 1738, 1692 cm⁻¹; ¹H-NMR (600 MHz, C₆D₆) δ = 6.71 (s, 1 H, ArH), 6.45 (s, 1 H, ArCH=CCH₃), 5.45 (dd, 1 H, J = 8.2, 2.3 Hz, CO₂CH), 4.15 (dd, 1 H, J = 10.8, 2.9 Hz, (CH₃)₂CCH(OH)), 3.81-3.78 (m, 1 H, CHOH(CHCH₃)), 3.65 (bs, 1 H, OH), 3.03 (qd, J = 6.9, 6.5 Hz, 1 H, CH₃CH(C=O)), 2.77 (ddd, J = 7.9, 4.0, 4.0 Hz, 1 H, CH₂CH-O(epoxide)CH), 2.62-2.58 (m, 1 H, CH₂CH-O(epoxide)CH), 2.40 (dd, J = 14.4, 10.8 Hz, 1 H, CH₂COO), 2.26 (bs, 1 H, OH), 2.21 (s, 3 H, CH₃Ar), 2.19 (dd, J = 14.4, 2.9 Hz, 1 H, CH₂COO), 2.05 (s, 3 H, ArCH=CCH₃), 1.86 (ddd, J = 15.2,

2.5, 2.5 Hz, 1 H, CH₂CH-O(epoxide)CH), 1.81-1.74 (m, 1 H, CH₂CH-O(epoxide)CH), 1.68 (ddd, J = 15.2, 7.6, 7.6 Hz, 1 H, CH₂CH-O(epoxide)CH), 1.53-1.49 (m, 1 H, CH₂CH-O(epoxide)CH), 1.40-1.15 (m, 5 H), 1.06 (d, 3 H, J = 7.0 Hz, CH₃CH(C=O)), 1.03 (s, 3 H, C(CH₃)₂), 0.97 (s, 3 H, C(CH₃)₂), 0.95 (d, J = 6.9 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz, C₆D₆) δ 219.0, 170.2, 164.7, 153.0, 137.5, 119.9, 116.6, 76.6, 75.2, 73.5, 57.2, 54.2, 52.9, 43.8, 39.1, 36.3, 31.7, 30.3, 27.3, 23.9, 21.1, 20.6, 18.7, 17.4, 15.7, 14.6; HRMS (FAB), calcd for C₂₆H₃₉N₆O₆S (M + Cs⁺) 626.1552, found 626.1531. 51: R_f = 0.35 (silica gel, 70% EtOAc in hexanes); [α]_D²⁵ -23.0 (c 0.10, CHCl₃); IR (film) ν_{max} 3416, 2925, 2855, 1732, 1688, 1457 1258, 1150 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 6.79 (s, 1 H, ArH), 6.57 (s, 1 H, ArCH=CCH₃), 5.82 (d, J = 8.0 Hz, 1 H, CO₂CH), 4.31 (dd, J = 10.5, 2.5 Hz, 1 H, (CH₃)₂CCH(OH)), 4.19-4.15 (m, 1 H, CHOH(CHCH₃)), 3.78 (bs, 1 H), 3.31 (qd, J = 7.0, 3.0 Hz, 1 H, CH₃CH(C=O)), 2.82 (ddd, J = 10.0, 4.2, 4.2 Hz, 1 H, CH₂CH-O(epoxide)CH), 2.76 (bs, 1 H), 2.55 (ddd, J = 9.0, 9.0, 4.5 Hz, 1 H, CH₂CH-O(epoxide)CH), 2.40 (dd, J = 13.0, 10.5, 1 H, CH₂COO), 2.33 (dd, J = 13.0, 2.5 Hz, 1 H, CH₂COO), 2.31 (s, 3 H, CH₃Ar), 2.20 (s, 3 H, ArCH=CCH₃), 1.97-1.92 (m, 1 H), 1.72 (ddd, J = 15.0, 8.5, 8.5 Hz, 1 H), 1.56 (ddd, J = 15.0, 4.5, 2.0 Hz, 1 H), 1.54-1.28 (m, 6 H), 1.17 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.13 (s, 3 H, C(CH₃)₂), 1.06 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂), 0.97 (s, 3 H, C(CH₃)₂); ¹³C NMR (150.9 MHz, C₆D₆) δ 221.7, 171.0, 165.5, 154.2, 138.3, 120.7, 117.6, 77.0, 74.8, 73.2, 57.7, 56.8, 52.4, 43.5, 39.5, 38.5,

33.0, 31.4, 28.3, 24.6, 21.6, 19.5, 19.2, 17.0, 15.7,
13.9; HRMS (FAB), calcd for C₂₆H₄₀NO₆S (M + H⁺) 494.2576,
found 494.2558. 52 (or 53): R_f = 0.3 (silica gel, 30%
EtOAc in hexanes); [α]_D²² -21.2 (c 0.17, CHCl₃); IR (film)
5 nmax 3477, 2926, 1740, 1686, 1465, 1259, 1060 cm⁻¹; ¹H NMR
(500 MHz, C₆D₆) δ 6.58 (s, 1 H, ArH), 5.44 (ddd, J =
10.5, 10.5, 5.0 Hz, 1 H, CH=CHCH₂), 5.35 (ddd, J = 10.5,
10.5, 5.5 Hz, 1 H, CH=CHCH₂), 5.23 (dd, J = 11.0, 2.0 Hz,
1 H, CO₂CH), 5.05-4.98 (m, 1 H), 4.44 (s, 1 H, ArCH-
10 O(epoxide)CCH₃), 4.35 (dd, J = 11.5, 2.0 Hz, 1 H,
(CH₃)₂CCH(OH)), 3.66-3.62 (m, 1 H, CHOH(CHCH₃)), 3.46 (s,
1 H, OH), 2.93 (q, J = 7.0 Hz, 1 H, CH₃CH(C=O)), 2.69
(ddd, J = 14.5, 11.0, 11.0 Hz, 1 H), 2.58 (dd, J = 14.0,
11.5 Hz, 1 H, CH₂COO), 2.17 (s, 3 H, CH₃Ar), 2.17-2.07 (m,
15 2 H), 2.06 (dd, J = 14.0, 2.0 Hz, 1 H, CH₂COO), 1.90-1.78
(m, 2 H), 1.55-1.28 (m, 4 H), 1.23 (s, 3 H, C(CH₃)₂), 1.20
(s, 3 H, C(CH₃)₂), 1.15 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)),
1.05 (s, 3 H, ArCH-O(epoxide)CCH₃), 1.01 (d, J = 7.0 Hz, 3
20 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, C₆D₆) δ 220.5, 169.7,
167.2, 151.0, 133.9, 124.2, 115.4, 74.5, 73.7, 71.9, 63.7,
59.2, 54.3, 40.9, 40.7, 38.2, 32.0, 29.1, 28.1, 26.9,
24.0, 18.3, 16.0, 15.6, 13.0 (two peaks overlapping); HRMS
(FAB), calcd for C₂₆H₄₀NO₆S (M + H⁺) 494.2576, found
25 494.2561. 53 (or 52): R_f = 0.25 (silica gel, 30% EtOAc
in hexanes); [α]_D²² +3.2 (c 0.25, CHCl₃); IR (film) nmax
3333, 2928, 2855, 1737, 1686, 1463, 1381, 1248 cm⁻¹; ¹H
NMR (500 MHz, C₆D₆) δ 6.62 (s, 1 H, ArH), 5.67 (d, J =
6.5 Hz, 1 H, (CH₃)₂CCH(OH)), 5.47 (dd, J = 11.5, 2.5 Hz, 1
H, CO₂CH), 5.45-5.37 (m, 1 H, CH=CHCH₂), 5.37-5.28 (m, 1

H, CH=CHCH₂), 4.44 (ddd, J = 12.0, 6.5, 2.5 Hz, 1 H,
 (CH₃)₂CCH(OH)), 4.22 (s, 1 H, ArCH-O(epoxide)CCH₃), 3.64
 (d, J = 4.5 Hz, 1 H, CHOH(CHCH₃)), 3.47 (s, 1 H,
 CHOH(CHCH₃)), 2.96 (q, J = 7.0 Hz, 1 H, CH₃CH(C=O)), 2.60
 5 (dd, J = 14.5, 12.0 Hz, 1 H, CH₂COO), 2.55 (ddd, J = 15.5,
 11.0, 11.0 Hz, 1 H), 2.20-2.02 (m, 2 H), 2.11 (s, 3 H,
 CH₃Ar), 1.99 (dd, J = 14.5, 2.5 Hz, 1 H, CH₂COO), 1.90-
 1.78 (m, 2 H), 1.58-1.49 (m, 1 H), 1.31 (s, 3 H, C(CH₃)₂),
 1.28-0.85 (m, 3H), 1.25 (s, 3 H, ArCH-O(epoxide)CCH₃),
 10 1.25 (s, 3 H, C(CH₃)₂), 1.21 (d, J = 7.0 Hz, 3 H,
 CH₃CH(C=O)), 1.03 (d, J = 7.5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR
 (125.7 MHz, C₆D₆) δ 219.8, 169.2, 167.1, 151.0, 133.2,
 124.7, 114.8, 74.8, 73.6, 70.8, 64.7, 57.5, 54.1, 40.2,
 39.6, 38.2, 31.8, 27.5, 27.2, 26.8, 24.1, 16.3, 15.9,
 15 15.2, 15.0, 7.1; HRMS (FAB), calcd for C₂₆H₄₀NO₆S (M + H+)
 494.2576, found 494.2594. 54 (or 55): R_f = 0.20 (silica
 gel, 70% EtOAc in hexanes); [α]_D²² -12.1 (c 0.14, CHCl₃);
 IR (film) ν_{max} 3410, 2925, 2854, 1735, 1686, 1642, 1464
 cm⁻¹; ¹H NMR (600 MHz, C₆D₆) δ 6.52 (s, 1 H, ArH), 5.72
 20 (d, J = 6.1 Hz, 1 H, OH), 5.42 (dd, J = 11.8, 2.0 Hz, 1 H,
 CO₂CH), 4.32-4.28 (m, 1 H, (CH₃)₂CCH(OH)), 4.05 (s, 1 H,
 ArCH(-O)(epoxide)CCH₃), 3.64 (bs, 1 H, CHOH(CHCH₃)), 2.92-
 2.86 (m, 1 H), 2.78-2.75 (m, 1 H), 2.66-2.63 (m, 1 H),
 2.58 (dd, J = 14.0, 11.8 Hz, 1 H, CH₂COO), 2.11 (d, J =
 25 15.4 Hz, 1 H), 2.03 (s, 3 H, CH₃Ar), 1.99 (dd, J = 14.0,
 2.8 Hz, 1 H, CH₂COO), 1.74-1.62 (m, 2 H), 1.61-1.52 (m, 2
 H), 1.50-1.05 (m, 5 H), 1.20 (s, 3 H, C(CH₃)₂), 1.19 (s, 3
 H, C(CH₃)₂), 1.18 (s, 3 H, ArCH-O(epoxide)CCH₃), 1.10 (d,
 J = 7.2 Hz, 3 H, CH₃CH(C=O)), 0.84 (d, J = 7.2 Hz, 3 H,

CH₃CHCH₂); ¹³C NMR (125.7 MHz, C₆D₆) δ 218.9, 170.3, 129.2, 115.9, 103.8, 74.7, 71.5, 65.6, 58.7, 57.9, 55.4, 55.2, 44.1, 40.7, 37.7, 32.2, 31.7, 29.1, 28.3, 24.5, 23.5, 18.9, 17.9, 17.5, 17.1, 7.2; HRMS (FAB), calcd for C₂₆H₄₀NO₇S (M + H⁺) 510.2526, found 510.2511. 55 (or 54): R_f = 0.15 (silica gel, 70% EtOAc in hexanes); [α]_D²² -10.0 (c 0.15, CHCl₃); IR (film) ν_{max} 3459, 2926, 2861, 1738, 1689, 1456 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 6.56 (d, J = 1.0 Hz, 1 H, ArH), 5.55 (d, J = 4.0 Hz, 1 H, OH), 5.22 (dd, J = 11.5, 2.0 Hz, 1 H, CO₂CH), 4.35 (s, 1 H, Arch-O(epoxide)CCH₃), 4.34-4.27 (m, 1 H, (CH₃)₂CCH(OH)), 3.71-3.68 (m, 1 H, CHOH(CHCH₃)), 3.04-2.98 (m, 1 H), 2.95 (qd, J = 7.0, 3.5 Hz, CH₃CH(C=O)), 2.88-2.83 (m, 1 H), 2.68-2.64 (m, 1 H), 2.61 (dd, J = 14.0, 11.5 Hz, 1 H, CH₂COO), 2.21-2.16 (m, 1 H), 2.14 (s, 3 H, CH₃Ar), 2.09 (dd, J = 14.0, 2.0 Hz, 1 H, CH₂COO), 1.81-1.65 (m, 3 H), 1.49-1.31 (m, 6 H), 1.25 (s, 3 H, C(CH₃)₂), 1.20 (s, 3 H, C(CH₃)₂), 1.12 (d, J = 6.5 Hz, 3 H, CH₃CH(C=O)), 0.96 (s, 3 H, Arch-O(epoxide)CCH₃), 0.88 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, C₆D₆) δ 219.7, 169.5, 150.9, 124.2, 115.0, 74.9, 73.6, 71.2, 63.2, 58.9, 56.7, 53.7, 40.0, 35.1, 31.2, 29.7, 30.7, 28.6, 28.0, 24.1, 22.7, 17.2, 16.3, 16.0, 12.3, 11.9; HRMS (FAB), calcd for C₂₆H₃₉CsNO₇S (M + Cs⁺) 642.1502, found 642.1521. 56: R_f = 0.10 (silica gel, 5% MeOH in Methylene chloride); [α]_D²² -110.0 (c 0.20, CHCl₃); IR (film) ν_{max} 3222, 2928, 2855, 1737, 1683, 1462 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.16 (s, 1 H, ArH), 5.84 (s, 1 H, Arch=CCH₃), 5.43 (ddd, J = 10.0, 10.0, 5.0 Hz, 1 H, CH=CHCH₂), 5.42-5.35 (m, 1 H, CH=CHCH₂), 5.40

(d, $J = 10.0$ Hz, 1 H, CO_2CH), 4.90 (d, 1 H, $J = 12.0$ Hz, $(\text{CH}_3)_2\text{CCH}(\text{OH})$), 3.76 (bs, 1 H), 3.75 (d, $J = 5.0$ Hz, 1 H, $\text{CHOH}(\text{CHCH}_3)$), 3.15 (q, $J = 7.0$ Hz, 1 H, $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 2.70 (dd, $J = 12.5, 12.5$ Hz, 1 H, CH_2COO), 2.50 (ddd, $J = 15.0, 10.0, 10.0$ Hz, 1 H, $\text{CH}=\text{CHCH}_2$), 2.21-2.12 (m, 2 H), 2.07 (dd, $J = 13.0, 2.5$ Hz, 1 H, CH_2COO), 1.97 (s, 3 H, CH_3Ar), 1.97-1.90 (m, 3 H), 1.63 (s, 3 H, $\text{ArCH}=\text{CCH}_3$), 1.62-1.54 (m, 2 H), 1.46 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.34 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.26-1.16 (m, 3 H), 1.20 (d, $J = 7.0$ Hz, 3 H, $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 1.06 (d, $J = 6.5$ Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, C_6D_6) δ 221.0, 169.5, 144.0, 143.2, 142.7, 133.2, 125.0, 111.0, 109.0, 75.8, 73.8, 71.5, 55.0, 40.1, 38.5, 32.6, 31.6, 29.5, 27.6, 26.9, 23.9, 17.2, 15.3, 14.9, 13.2, 12.8; HRMS (FAB), calcd for $\text{C}_{26}\text{H}_{39}\text{CsNO}_6\text{S}$ 626.1552 ($\text{M} + \text{Cs}^+$) 626.1552, found 626.1584. 57: $R_f = 0.05$ (silica gel, 5% MeOH in Methylene chloride); $[\alpha]_{\text{D}}^{25} -58.0$ (c 0.10, CHCl_3); IR (film) ν_{max} 3340, 2921, 2851, 1736, 1686, 1459, 1248 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.13 (s, 1 H, ArH), 6.84 (s, 1 H, $\text{ArCH}=\text{CCH}_3$), 5.34 (d, $J = 11.0$ Hz, 1 H, CO_2CH), 4.55 (dd, 1 H, $J = 10.0, 1.0$ Hz, $(\text{CH}_3)_2\text{CCH}(\text{OH})$), 3.74 (dd, $J = 5.5, 2.0$ Hz, 1 H, $\text{CHOH}(\text{CHCH}_3)$), 3.25 (qd, $J = 6.5, 1.5$ Hz, 1 H, $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 3.10-2.94 (m, 1 H), 2.70-2.64 (m, 2 H), 2.50 (dd, $J = 12.5, 12.5$ Hz, 1 H), 2.25 (d, $J = 14.0$ Hz, 1 H, CH_2COO), 2.15 (dd, $J = 14.0, 2.5$ Hz, 1 H), 2.10 (s, 3 H, CH_3Ar), 1.93-1.15 (m, 7 H), 1.46 (s, 3 H, $\text{ArCH}=\text{CCH}_3$), 1.25 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.20 (d, $J = 7.0$ Hz, 3 H, $\text{CH}_3\text{CH}(\text{C}=\text{O})$), 1.04 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.01 (d, $J = 7.0$ Hz, 3 H, CH_3CHCH_2); HRMS (FAB), calcd for $\text{C}_{26}\text{H}_{39}\text{CsNO}_7\text{S}$ ($\text{M} + \text{Cs}^+$) 642.1502, found 642.1522.

Synthesis of Compounds 54, 55, and 57 as illustrated in Figure 8. Oxidation of Epothilone A (1) with mCPBA. A solution of epothilone A (1) (3.0 mg, 0.006 mmol) in CHCl₃ (120 mL, 0.05 M) was reacted with meta-chloroperbenzoic acid (mCPBA, 57-86%, 1.1 mg, 0.0023-0.0032 mmol, 0.8-1.1 equiv; Aldrich), at -20 to 0 °C, according to the procedure described for the epoxidation of 37, resulting in the formation of bis(epoxides) 54 (or 55) (1.1 mg, 35%) and 55 (or 54) (1.0 mg, 32%) along with sulfoxide 57 (0.2 mg, 6%).

Synthesis of Epothilones 58-60 as illustrated in Figure 9. Epoxidation of trans-Dihydroxy Lactone 50. Procedure A: A solution of trans-dihydroxy lactone 50 (20 mg, 0.042 mmol) in CHCl₃ (4.0 mL) was treated with meta-chloroperbenzoic acid (mCPBA, 57-86%, 11.0 mg, 0.036-0.054 mmol, 0.9-1.3 equiv) at -20 to 0 °C, according to the procedure described for the epoxidation of compound 37, to give a epothilones 58 (or 59) (1.0 mg, 5%), 59 (or 58) (1.0 mg, 5%), and 60 (12 mg, 60%) (stereochemistry unassigned for all three), after preparative thin layer chromatography (250 mm silica gel plate, 70% EtOAc in hexanes). Procedure B: According to procedure B for the epoxidation of cis-dihydroxy lactone 49, a solution of trans-dihydroxy lactone 50 (10.0 mg, 0.02 mmol) in Methylene chloride (1.0 mL) was reacted with a solution of dimethyldioxirane (ca 0.1 M, 0.2 mL, ca 1.0 equiv) in acetone at 0 °C, and after preparative thin layer

chromatography (250 mm silica gel plate, 70% EtOAc in hexanes), epothilones 58 (or 59) (1.0 mg, 10%), 59 (or 58) (1.0 mg, 10%), and 60 (4.0 mg, 40%) were obtained.

Procedure C. As described in procedure B for the epoxidation of trans-hydroxy lactone 37, trans-dihydroxy lactone 50 (5.1 mg, 0.01 mol) in MeCN (100 mL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 60 mL), excess 1,1,1-trifluoroacetone (100 mL), Oxone® (32 mg, 0.05 mmol, 5.0 equiv) and NaHCO₃ (7.0 mg, 0.08 mmol, 8.0 equiv), to yield, after purification by preparative thin layer chromatography (250 mm silica gel plate, ether), epothilones 58 (or 59) (2.3 mg, 45%) and 59 (or 58) (1.8 mg, 35%). 58 (or 59): R_f = 0.15 (silica gel, ether); [α]_D²⁵ -23.3 (c 0.40, CHCl₃); IR (film) ν_{max} 3454, 2926, 2856, 1731, 1690, 1464, 1376, 1259, 1151, 980 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 6.73 (s, 1 H, ArH), 6.53 (s, 1 H, ArCH=C(CH₃)), 5.54 (dd, J = 8.0, 2.0 Hz, 1 H, CO₂CH), 4.18 (d, J = 10.0 Hz, 1 H, (CH₃)₂CCH(OH)), 3.87 (dd, J = 4.5, 2.0 Hz, 1 H, CHOH(CHCH₃)), 3.43 (bs, 1 H), 3.13 (dq, J = 7.0, 7.0 Hz, 1 H, CH₃CH(C=O)), 2.74-2.72 (m, 1 H), 2.63-2.60 (m, 1 H), 2.45 (dd, J = 15.0, 10.5 Hz, 1 H, CH₂COO), 2.33 (dd, J = 15.0, 3.0 Hz, 1 H, CH₂COO), 2.32-2.24 (m, 1 H), 2.28 (s, 3 H, CH₃Ar), 2.12 (s, 3 H, ArCH=CCH₃), 2.00 (ddd, J = 15.0, 3.0, 2.5 Hz, 1 H), 1.75-1.65 (m, 3 H), 1.60-0.98 (m, 4 H), 1.18 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.10 (s, 3 H, C(CH₃)₂), 1.05 (s, 3 H, C(CH₃)₂), 0.97 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, C₆D₆) δ 217.2, 170.3, 164.6, 153.2, 137.0, 120.4, 116.9, 76.7,

75.6, 72.8, 58.0, 56.0, 53.0, 44.7, 38.8, 36.5, 35.8, 32.0, 30.3, 30.1, 22.6, 21.0, 20.9, 17.1, 15.3, 14.9; HRMS (FAB), calcd for C₂₆H₃₉CsNO₆S (M + Cs⁺) 626.1552, found 626.1538. 59 (or 58): R_f = 0.2 (silica gel, ether); [α]_D²⁵ -25.3 (c 0.30, CHCl₃); IR (film) ν_{max} 3419, 2923, 1732, 1691, 1464, 1259 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 6.82 (s, 1 H, ArH), 6.56 (s, 1 H, ArCH=C(CH₃)), 5.53 (dd, J = 7.5, 3.5 Hz, 1 H, CO₂CH), 4.47 (d, J = 8.5 Hz, 1 H, (CH₃)₂CCH(OH)), 3.94 (bs, 1 H, CHOH(CHCH₃)), 3.65-3.58 (m, 1 H), 3.35 (dq, J = 6.5, 6.5 Hz, 1 H, CH₃CH(C=O)), 2.73-2.65 (m, 1 H), 2.65-2.61 (m, 1 H), 2.52-2.46 (m, 1 H), 2.41 (dd, J = 14.0, 9.5 Hz, 1 H, CH₂COO), 2.33 (dd, J = 14.0, 4.0 Hz, 1 H, CH₂COO), 2.31 (s, 3 H, CH₃Ar), 2.03 (s, 3 H, ArCH=CCH₃), 1.91-1.81 (m, 2 H), 1.78-1.53 (m, 4 H), 1.41-1.32 (m, 2 H), 1.22 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.21 (s, 3 H, C(CH₃)₂), 1.08 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂), 1.05 (s, 3 H, C(CH₃)₂); ¹³C NMR (150.9 MHz, C₆D₆) δ 215.7, 167.6, 161.7, 149.8, 133.8, 116.6, 113.4, 73.8, 73.2, 70.1, 55.2, 52.4, 49.9, 41.7, 36.4, 34.0, 32.3, 28.0, 27.8, 27.4, 19.9, 17.8, 15.8, 14.6, 13.0, 12.3; HRMS (FAB), calcd for C₂₆H₃₉CsNO₆S (M + Cs⁺) 626.1552, found 626.1531. 60: R_f = 0.6 (silica gel, 70% EtOAc in hexanes); [α]_D²⁵ -28.3 (c 0.30, CHCl₃); IR (film) ν_{max} 3472, 2928, 1735, 1691, 1466 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 6.67 (s, 1 H, ArH), 5.48-5.41 (m, 1 H, CH=CHCH₂), 5.36-5.23 (m, 2 H, CH=CHCH₂ and CO₂CH), 4.36-4.30 (m, 1 H, (CH₃)₂CCH(OH)), 3.79-3.73 (m, 1 H), 3.63-3.58 (m, 1 H), 3.17-3.10 (m, 1 H, CH₃CH(C=O)), 2.81 (bs, 1 H), 2.53 (dd, J = 15.0, 10.5 Hz, 1 H, CH₂COO), 2.40-2.29 (m, 2 H), 2.26-

2.19 (m, 2 H), 2.25 (s, 3 H, CH₃Ar), 2.20-1.95 (m, 1 H),
 1.80-1.72 (m, 1 H), 1.62-1.53 (m, 1 H), 1.46-1.33 (m, 2
 H), 1.20 (d, J = 6.5 Hz, 3 H, CH₃CH(C=O)), 1.13 (s, 3 H,
 C(CH₃)₂), 1.10 (s, 3 H, C(CH₃)₂), 1.08 (d, J = 7.0 Hz, 3
 5 H, CH₃CHCH₂), 1.06 (s, 3 H, ArCH-O(epoxide)CCH₃); ¹³C NMR
 (125.7 MHz, C₆D₆) δ 219.7, 169.6, 166.9, 151.3, 135.4,
 124.6, 115.8, 78.3, 72.8, 72.6, 64.2, 59.1, 53.3, 43.4,
 40.2, 38.8, 34.3, 33.1, 31.4, 27.5, 21.8, 19.8, 18.9,
 16.5, 15.3, 14.0; HRMS (FAB), calcd for C₂₆H₄₀NO₆S (M +
 10 H⁺) 494.2576, found 494.2587.

**Synthesis of Dihydroxy Ester 61 as illustrated in
 Figure 10.** Desilylation of Compound 47. Silyl ether 47
 (48 mg, 0.079 mmol) was treated with a freshly prepared
 15 solution of 20% (v/v) trifluoroacetic acid (TFA)-Methylene
 chloride (1.6 mL, 0.05 M), according to the procedure
 described for the desilylation of compound 3, to yield,
 after flash column chromatography (silica gel, 5% & 50%
 EtOAc in hexanes), dihydroxy ester 61 (35 mg, 90%). R_f =
 20 0.68 (silica gel, 50% EtOAc in hexanes); [α]_D²² -18.0 (c
 0.40, CHCl₃); IR (film) ν_{max} 3420, 2931, 1732, 1383, 1177,
 979 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.97 (s, 1 H, ArH),
 6.54 (s, 1 H, ArCH=CCH₃), 5.82-5.70 (m, 2 H, 2 x
 CH₂CH=CH₂), 5.37 (dd, J = 7.0, 7.0 Hz, 1 H, CO₂CH), 5.10
 25 (d, J = 17.0 Hz, 1 H, CH₂CH=CH₂), 5.07 (d, J = 10.0 Hz, 1
 H, CH₂CH=CH₂), 5.00 (d, J = 17.0 Hz, 1 H, CH₂CH=CH₂), 4.95
 (d, J = 10.0 Hz, 1 H, CH₂CH=CH₂), 4.24 (dd, J = 10.0, 2.0
 Hz, 1 H, (CH₃)₂CCHOH), 3.50 (dd, J = 8.0, 3.0 Hz, 1 H,
 CHOH(CHCH₃)), 3.26 (qd, J = 6.5, 2.5 Hz, 1 H, CH₃CH(C=O)),

2.70 (s, 3 H, CH₃Ar), 2.52-2.46 (m, 2 H), 2.41 (dd, J = 16.5, 10.5 Hz, 1 H, CH₂COO), 2.08 (s, 3 H, ArCH=CCH₃), 2.08-1.99 (m, 2 H, CH₂CH=CH₂), 1.60-1.06 (m, 6 H), 1.17 (s, 6 H, C(CH₃)₂), 1.07 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 0.97 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 221.5, 171.9, 164.7, 152.1, 138.7, 136.7, 133.1, 120.9, 117.9, 116.4, 114.5, 78.7, 74.8, 72.3, 52.1, 41.4, 37.5, 36.8, 35.0, 33.8, 32.3, 25.7, 21.5, 19.1, 19.0, 15.2, 14.7, 11.5; HRMS (FAB), calcd for C₂₈H₄₃CsNO₅S (M + Cs⁺) 638.1916, found 638.1902.

Synthesis of Dihydroxy Lactones 62 and 63 as illustrated in Figure 10. Olefin Metathesis of Dihydroxy Ester 61. A solution of compound 61 (48 mg, 0.095 mmol) in Methylene chloride (20 mL, 0.005 M) was treated with bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (RuCl₂(=CHPh)(PCy₃)₂, 16 mg, 0.019 mmol, 0.2 equiv; Figure 10), according to the procedure described for the cyclization of 25, producing dihydroxy lactones 62 (9.1 mg, 20%) and 63 (32 mg, 69%), after preparative thin layer chromatography (0.5 mm silica gel plate, 33% EtOAc in hexanes). 62: R_f = 0.30 (silica gel, 6% MeOH in Methylene chloride); [α]_D²² -93.1 (c 0.10, CHCl₃); IR (thin film) ν_{max} 3450, 2929, 1735, 1685, 1464, 1380, 1250, 1182, 1045, 978, 732 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.96 (s, 1 H, ArH), 6.51 (s, 1 H, ArCH=CCH₃), 5.58 (dd, J = 9.5, 2.0 Hz, 1 H, CO₂CH), 5.56 (ddd, J = 9.8, 9.8, 6.5 Hz, 1 H, CH=CHCH₂), 5.37 (ddd, J = 9.8, 9.8, 4.5 Hz, 1 H, CH=CHCH₂), 4.25 (d, J = 10.0 Hz, 1 H,

(CH₃)₂CCCH(OH)), 3.55 (d, J = 9.6 Hz, 1 H, CHOH(CHCH₃)),
 3.39 (bs, 1 H, OH), 3.31 (q, J = 6.9 Hz, 1 H, CH₃CH(C=O)),
 2.99 (bs, 1 H, OH), 2.71 (s, 3 H, CH₃Ar), 2.69-2.61 (m, 1
 H, CH=CHCH₂), 2.59 (dd, J = 16.3, 1.5 Hz, 1 H, CH₂COO),
 5 2.41 (dd, J = 16.3, 10.0 Hz, 1 H, CH₂COO), 2.45-2.35 (m, 1
 H, CH=CHCH₂), 2.20-2.10 (m, 1 H, CH=CHCH₂), 2.08 (s, 3 H,
 ArCH=CCH₃), 1.98-1.90 (m, 1 H, CH=CHCH₂), 1.59-1.50 (m, 1
 H), 1.49-1.30 (m, 4 H), 1.17 (s, 3 H, C(CH₃)₂), 1.11 (d, J
 = 6.9 Hz, 3 H, CH₃CH(C=O)), 1.03 (s, 3 H, C(CH₃)₂), 1.01
 10 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz, CDCl₃)
 d 222.2, 171.1, 165.2, 153.5, 139.5, 133.2, 125.1, 120.0,
 116.7, 78.4, 74.1, 72.9, 52.5, 40.7, 39.5, 37.9, 34.5,
 32.7, 31.3, 27.6, 24.7, 22.2, 18.9, 17.5, 15.5, 15.3; HRMS
 (FAB), calcd for C₂₆H₃₉NO₅S (M + H⁺) 478.2627, found
 15 478.2610. 63: R_f = 0.69 (silica gel, 50% EtOAc in
 hexanes); [α]_D²⁵ -68.3 (c 1.30, CHCl₃); IR (film) ν_{max}
 3498, 2932, 1730, 1694, 1383, 1260, 1154, 1076, 1043, 974,
 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) d 6.95 (s, 1 H, ArH),
 6.49 (s, 1 H, ArCH=CCH₃), 5.50 (t, J = 6.5 Hz, 1 H,
 CO₂CH), 5.48 (ddd, J = 15.0, 7.0, 6.0 Hz, 1 H, CH=CHCH₂),
 20 5.36 (ddd, J = 15.0, 6.5, 6.5 Hz, 1 H, CH=CHCH₂), 4.24
 (dd, J = 10.5, 1.0 Hz, 1 H, (CH₃)₂CCCHOH), 3.55 (d, J = 9.5
 Hz, 1 H, CHOH(CHCH₃)), 3.37 (q, J = 7.0 Hz, 1 H,
 CH₃CH(C=O)), 2.69 (s, 3 H, CH₃Ar), 2.58 (dd, J = 15.5, 1.5
 Hz, 1 H, CH₂COO), 2.50-2.48 (m, 2 H, CH=CHCH₂), 2.39 (dd,
 25 J = 15.5, 10.5 Hz, 1 H, CH₂COO), 2.16-2.08 (m, 1 H,
 CH=CHCH₂), 2.08 (s, 3 H, ArCH=CCH₃), 1.97-1.91 (m, 1 H,
 CH=CHCH₂), 1.62-1.56 (m, 1 H), 1.41-1.11 (m, 4 H), 1.20
 (s, 3 H, C(CH₃)₂), 1.12 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)),

1.03 (s, 3 H, C(CH₃)₂), 0.98 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 221.8, 171.1, 164.8, 152.1, 136.7, 134.2, 124.9, 119.8, 116.4, 78.1, 74.6, 73.2, 52.8, 40.9, 38.3, 36.1, 34.6, 32.9, 32.9, 24.9, 22.9, 19.2, 17.7, 16.0, 15.5, 11.5; HRMS (FAB), calcd for C₂₆H₃₉NO₅S (M + Cs⁺) 610.1603, found 610.1587.

Synthesis of Epothilones 64-65 as illustrated in Figure 10. Epoxidation of cis-Dihydroxy Lactone 62.

Procedure A: A solution of cis-dihydroxy lactone 62 (10.0 mg, 0.021 mmol) in CHCl₃ (210 mL) was treated with meta-chloroperbenzoic acid (mCPBA, 57-86%, 5.0 mg, 0.0165-0.0252 mmol, 0.8-1.2 equiv) at -20 ± 0 °C, according to the procedure described for the epoxidation of compound 37, to produce, after preparative thin layer chromatography (250 mm silica gel plate, 70% EtOAc in hexanes), epothilones 64 (or 65) (2.6 mg, 25%) and 65 (or 64) (2.4 mg, 23%) (stereochemistry unassigned for all three). Procedure B. As described in procedure B for the epoxidation of trans-hydroxy lactone 37, cis-dihydroxy lactone 62 (10.0 mg, 0.021 mmol) in MeCN (400 mL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 200 mL), excess 1,1,1-trifluoroacetone (150 mL), Oxone® (65 mg, 0.105 mmol, 5.0 equiv) and NaHCO₃ (14 mg, 0.168 mmol, 8.0 equiv), to yield, after purification by preparative thin layer chromatography (250 mm silica gel plate, ether), epothilones 64 (or 65) (6.0 mg, 58%) and 65 (or 64) (3.0 mg, 29%). 64 (or 65): R_f = 0.23 (silica gel, 6% MeOH in

Methylene chloride); $[\alpha]_{22D} -20.0$ (c 0.20, CHCl₃); IR
 (thin film) ν_{max} 3448, 2919, 1725, 1684, 1455, 1378, 1284,
 1149, 1061, 1020, 973, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ
 6.99 (s, 1 H, ArH), 6.68 (s, 1 H, ArCH=CCH₃), 5.64-5.61
 5 (m, 1 H, CO₂CH), 4.43 (d, J = 2.1 Hz, 1 H, (CH₃)₂CCH(OH),
 4.29 (ddd, J = 7.6, 2.5, 2.5 Hz, 1 H, (CH₃)₂CCH(OH)), 3.82
 (d, J = 8.2 Hz, 1 H, CHOH(CHCH₃)), 3.35 (bs, 1 H,
 CHOH(CHCH₃), 3.22 (q, J = 7.0 Hz, 1 H, CH₃CH(C=O)), 3.14
 (ddd, J = 10.3, 4.1, 3.2 Hz, 1 H, CH₂CH-O(epoxide)CH),
 10 2.90 (ddd, J = 10.3, 4.3, 2.3 Hz, 1 H, CH₂CH-
 O(epoxide)CH), 2.71 (s, 3 H, CH₃Ar), 2.54 (dd, J = 13.7,
 7.6 Hz, 1 H, CH₂COO), 2.51 (dd, J = 13.7, 2.5 Hz, 1 H,
 CH₂COO), 2.21-2.19 (m, 1 H), 2.18 (s, 3 H, ArCH=CCH₃),
 1.94 (ddd, J = 15.3, 10.3, 3.7 Hz, 1 H), 1.77-1.69 (m, 2
 15 H), 1.60-1.00 (m, 5 H), 1.15 (s, 3 H, C(CH₃)₂), 1.14 (d, J
 = 6.9 Hz, 3 H, CH₃CH(C=O)), 1.06 (s, 3 H, C(CH₃)₂), 1.02
 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz,
 CHCl₃) δ 221.8, 172.1, 165.1, 152.6, 134.7, 119.8, 116.8,
 76.0, 74.4, 72.8, 56.4, 53.8, 53.0, 40.2, 39.1, 34.1,
 20 32.7, 29.4, 27.8, 22.7, 20.9, 19.0, 16.1, 15.9, 15.0,
 11.8; HRMS (FAB), calcd for C₂₆H₄₀NO₆S (M + H⁺) 494.2576,
 found 494.2587. 65 (or 64): R_f = 0.22 (silica gel, 6%
 MeOH in Methylene chloride); $[\alpha]_{22D} -42.5$ (c 0.20, CHCl₃);
 IR (thin film) ν_{max} 3384, 2890, 1738, 1685, 1451, 1375,
 25 1155, 1061, 1064 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.99 (s,
 1 H, ArH), 6.58 (s, 1 H, ArCH=CCH₃), 5.88 (d, J = 10.4 Hz,
 1 H, CO₂CH), 4.74 (d, J = 9.8 Hz, 1 H, (CH₃)₂CCH(OH)),
 3.70-3.65 (m, 2 H, CHOH(CHCH₃) and OH), 3.45-3.40 (m, 2 H,
 CH₃CH(C=O) and OH), 3.19 (ddd, J = 9.7, 3.8, 2.1 Hz, 1 H,

CH₂CH-O(epoxide)CH), 3.08 (ddd, J = 9.0, 4.5, 4.5 Hz, 1 H, CH₂CH-O(epoxide)CH), 2.71 (s, 3 H, CH₃Ar), 2.51 (d, J = 13.8, 1 H, CH₂COO), 2.45 (dd, J = 13.7, 9.8 Hz, 1 H, CH₂COO), 2.18-2.02 (m, 2 H), 2.11 (s, 3 H, ArCH=CCH₃), 1.80-0.96 (m, 7 H), 1.16 (s, 3 H, C(CH₃)₂), 1.13 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.05 (s, 3 H, C(CH₃)₂), 1.03 (d, J = 6.8 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz, CHCl₃) δ 222.2, 171.1, 164.8, 151.8, 136.6, 120.3, 116.7, 76.9, 73.7, 72.9, 56.6, 54.8, 52.8, 40.2, 38.8, 34.1, 33.0, 31.7, 25.0, 23.3, 20.4, 19.4, 16.7, 15.8, 15.6, 11.9; HRMS (FAB), calcd for C₂₆H₃₉CsNO₆S (M + Cs⁺) 626.1552, found 626.1573.

Synthesis of Epothilones 67-69 as illustrated in Figure 10. Epoxidation of trans-Dihydroxy Lactone 63. Procedure A. A solution of trans-dihydroxy lactone 63 (17.0 mg, 0.033 mmol) in CHCl₃ (2.0 mL) was treated with meta-chloroperbenzoic acid (mCPBA, 57-86%, 8.9 mg, 0.029-0.044 mmol, 0.9-1.3 equiv) at -20 to 0 °C, according to the procedure described for the synthesis of epoxide 37, to produce, after preparative thin layer chromatography (250 mm silica gel plate, 70% EtOAc in hexanes), epothilones 67 (or 68) (4.2 mg, 24%), 68 (or 67) (3.3 mg, 19%) and 69 (5.4 mg, 31%) (stereochemistry unassigned for all three). Procedure B. As described in procedure C for the epoxidation of cis-lactone 49, trans-dihydroxy lactone 63 (6.0 mg, 0.0126 mmol) in MeCN (240 mL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 90 mL), 1,1,1-

trifluoroacetone (90 mL), Oxone® (40 mg, 0.063 mmol, 5.0 equiv) and NaHCO₃ (8.4 mg, 0.100 mmol, 8.0 equiv), to yield, after purification by preparative thin layer chromatography (250 mm silica gel plate, ether),

5 epothilones 67 (or 68) (2.7 mg, 44%) and 68 (or 67) (1.3 mg, 21%). 67 (or 68): R_f = 0.47 (silica gel, 50% EtOAc in hexanes); [α]_D²² -27.3 (c 0.30, CHCl₃); IR (film) ν_{max} 3459, 2932, 1732, 1152, 978 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.97 (s, 1H, ArH), 6.57 (s, 1H, ArCH=CCH₃), 5.72 (d, J = 10.4 Hz, 1H, CO₂CH), 4.41 (d, J = 9.8 Hz, 1H, (CH₃)₂CCH(OH)), 4.27 (bs, 1H, OH), 3.76 (d, J = 6.1 Hz, 1H, CHOH(CHCH₃)), 3.27 (q, J = 7.0 Hz, 1H, CH₃CH(C=O)), 2.94-2.88 (m, 1H), 2.75-2.71 (m, 1H), 2.70 (s, 3H, CH₃Ar), 2.49 (d, J = 12.9 Hz, 1H, CH₂COO), 2.41 (dd, J = 12.9, 9.8 Hz, 1H, CH₂COO), 2.18-2.11 (m, 1H), 2.09 (s, 3H, ArCH=CCH₃), 1.95-1.87 (m, 1H), 1.80-1.00 (m, 5H), 1.16 (s, 3H, C(CH₃)₂), 1.14 (d, 3H, J = 6.9 Hz, CH₃CH(C=O)), 1.04 (s, 3H, C(CH₃)₂), 0.92 (d, 3H, J = 6.9 Hz, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 220.4, 171.9, 164.7, 151.9, 136.5, 120.2, 116.6, 76.9, 74.5, 73.6, 58.1, 56.0, 53.1, 42.2, 39.2, 36.2, 34.7, 33.1, 29.4, 22.4, 21.9, 19.3, 16.2, 15.2, 13.7, 12.4; ; HRMS (FAB), calcd for C₂₆H₄₀NO₆S (M + H⁺) 494.2576, found 494.2561. 68 (or 67): R_f = 0.46 (silica gel, 50% EtOAc in hexanes); [α]_D²² -55.2 (c 0.25, CHCl₃); IR (film) ν_{max} 3442, 2931, 1731, 1687, 1153, 982, 732 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.97 (s, 1H, ArH), 6.57 (s, 1H, ArCH=CCH₃), 5.56 (dd, J = 8.6, 3.1 Hz, 1H, CO₂CH), 4.23 (d, J = 9.3 Hz, 1H, (CH₃)₂CCH(OH)), 3.73 (dd, J = 7.4, 1.1 Hz, 1H,

10

15

20

25

CHOH(CHCH₃)), 3.57 (bs, 1 H), 3.34 (dq, J = 7.0, 1.3 Hz, CH₃CH(C=O)), 3.12 (bs, 1 H), 2.76 (dt, J = 5.5, 2.2 Hz, 2 H), 2.72-2.68 (m, 1 H), 2.71 (s, 3 H, CH₃Ar), 2.61 (dd, J = 15.4, 1.6 Hz, 1 H, CH₂COO), 2.41 (dd, J = 15.4, 10.6 Hz, 1 H, CH₂COO), 2.15 (ddd, J = 15.0, 5.1, 3.5 Hz, 1 H), 2.07 (s, 3 H, ArCH=CCH₃), 1.91-1.86 (m, 1 H), 1.76-1.17 (m, 5 H), 1.29 (s, 3 H, C(CH₃)₂), 1.30 (s, 3 H, C(CH₃)₂), 1.12 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 0.95 (d, J = 6.7 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 221.2, 171.2, 164.9, 151.8, 135.9, 120.1, 116.6, 77.1, 74.0, 72.8, 58.7, 55.8, 52.7, 42.3, 38.4, 35.3, 35.1, 33.0, 32.0, 22.6, 22.0, 19.3, 18.5, 15.5, 15.2, 12.2; HRMS (FAB), calcd for C₂₆H₄₀NO₆S (M + H⁺) 494.2562, found 494.2576. 69: R_f = 0.67 (silica gel, 50% EtOAc in hexanes); [α]_D²⁵ -30.5 (c = 0.40, CHCl₃); IR (film) ν_{max} 3500, 2932, 1732, 1693, 1184, 975 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.95 (s, 1 H, ArH), 5.51 (ddd, J = 14.3, 7.0, 7.0 Hz, 1 H, CH=CHCH₂), 5.37 (ddd, J = 14.3, 7.1, 7.1 Hz, 1 H, CH=CHCH₂), 5.16 (dd, J = 9.2, 3.4 Hz, 1 H, CO₂CH), 4.20 (d, J = 10.7 Hz, 1 H, (CH₃)₂CCH(OH)), 4.16 (s, 1 H, OH), 3.48 (d, J = 9.2 Hz, 1 H, CHOH(CHCH₃)), 3.37 (q, J = 6.9 Hz, 1 H, CH₃CH(C=O)), 2.70 (s, 3 H, CH₃Ar), 2.62 (d, J = 15.7 Hz, 1 H, CH₂COO), 2.60-2.54 (m, 1 H), 2.50-2.43 (m, 1 H), 2.38 (dd, J = 15.7, 10.7 Hz, 1 H, CH₂COO), 2.23-2.15 (m, 1 H, CH=CHCH₂), 2.00-1.92 (m, 1 H, CH=CHCH₂), 1.80-1.00 (m, 5 H), 1.24 (s, 3 H, C(CH₃)₂), 1.20 (s, 3 H, C(CH₃)₂), 1.10 (d, 3 H, J = 6.9 Hz, CH₃CH(C=O)), 1.02 (s, 3 H, ArCH-O(epoxide)CCH₃), 0.98 (d, 3 H, J = 6.7 Hz, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 221.4, 170.9, 166.3, 150.6, 135.4, 124.3, 115.4,

74.8, 74.1, 73.1, 63.0, 58.8, 52.7, 41.1, 38.1, 34.8, 33.5, 33.2, 32.9, 25.2, 22.9, 19.3, 18.1, 16.1, 13.4, 11.7; HRMS (FAB), calcd for C₂₆H₄₀NO₆S (M + H⁺) 494.2576, found 494.2587.

5

Synthesis of Alcohol 85 as illustrated in Figure 12. Allylboration of Keto Aldehyde 84. Aldehyde 84 (16.0 g, 0.125 mol; Inuka, T.; Yoshizawa, R. J. Org. Chem. 1967, 32, 404-407) was dissolved in ether (400 mL) and cooled to -100 °C. To this solution was added (+)-diisopinocampheylallylborane (800 mL, 0.15 M in pentane, 0.125 mol, 1.0 equiv) by cannulation during 45 min. [(+)-Diisopinocampheylallylborane in pentane is prepared by the adaptation of the standard methods reported by Brown]. Allylmagnesium bromide (66.0 mL, 1 M solution in ether, 0.066 mol) was added dropwise to a well stirred solution of (-)-B-methoxydiisopinocampheyl borane (20.9 g, 0.066 mol) in ether (400 mL) at 0 °C. After the completion of the addition, the reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The residue was extracted with pentane (3 x 400 mL) under argon and stirring was discontinued to allow precipitation of the magnesium salts. The clear pentane solution was cannulated into another flask using a double ended needle through a Kramer filter and used without further purification. After the addition was complete, the mixture was stirred at the same temperature for 30 min. Methanol (20 mL) was added at -100 °C, and the reaction mixture was allowed to reach room

10

15

20

25

temperature. To this solution was added saturated aqueous NaHCO₃ solution (200 mL), followed by H₂O₂ (80 mL of 50% solution in H₂O) and the reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture was extracted with EtOAc (3 x 200 mL), and the organic extracts were combined, washed with saturated aqueous NH₄Cl solution (100 mL) and dried (Na₂SO₄). Evaporation of the solvents followed by flash column chromatography (silica gel, 3% acetone in Methylene chloride) resulted in pure alcohol 85 (14.6 g, 74%). 85: colorless oil; R_f = 0.20 (silica gel, 3% acetone in Methylene chloride); [α]_D²⁵ -4.0 (c 1.5, CHCl₃); IR (thin film) ν_{max} 3492, 2976, 2939, 1699, 1641, 1469, 1379, 1087, 1020, 990, 973, 914 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.85-5.80 (m, 1 H, CH=CH₂), 5.11-5.07 (m, 2 H, CH=CH₂), 3.73 (dd, J = 10.5, 2.0 Hz, 1 H, CHOH), 2.54-2.40 (m, 3 H), 2.25-2.18 (m, 1 H), 2.03-1.96 (m, 1 H), 1.14 (s, 3 H, C(CH₃)₂), 1.10 (s, 3 H, C(CH₃)₂), 0.99 (t, J = 7.0 Hz, 3 H, CH₃CH₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 217.2, 135.6, 117.7, 75.5, 51.2, 36.4, 31.3, 21.8, 19.5, 7.8; FAB HRMS (NBA/NaI) m/e 193.1200, M + Na⁺ calcd for C₁₀H₁₈O₂ 193.1204.

Synthesis of Ketone 86 as illustrated in Figure 12. Silylation of Alcohol 85. Alcohol 85 (11.0 g, 0.0647 mol) was dissolved in Methylene chloride (200 mL), the solution was cooled at -78 °C, and 2,6-lutidine (10.5 mL, 0.0906 mol, 1.4 equiv) was added. After stirring for 5 min at that temperature, tert-butyldimethylsilyl triflate (19.3 mL, 0.0841 mol, 1.3 equiv) was added dropwise and

the reaction mixture was allowed to stir at -78 °C for 45 min, after which time no starting material was detected by TLC. Saturated aqueous NH₄Cl solution (30 mL) was added, and the reaction mixture was allowed to warm up to room temperature. The organic phase was separated, and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered through celite and the solvents were removed under reduced pressure. Purification by flash column chromatography (silica gel, 2 to 10% ether in hexanes) gave pure 86 (18.0 g, 98%): R_f = 0.75 (silica gel, 20% ether in hexanes); [α]_D²⁵ +2.6 (c 0.8, CHCl₃); IR (thin film) ν_{max} 2935, 1705, 1467, 1362, 1254, 1089, 911, 836, 775 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.78-5.71 (m, 1 H, CH=CH₂), 5.01-4.94 (m, 2 H, CH=CH₂), 3.97 (dd, J = 6.2, 5.2 Hz, 1 H, CHOSi), 2.54 (dq, J = 14.3, 7.2 Hz, 1 H, CH₂CH₃), 2.44 (dq, J = 14.2, 7.1 Hz, 1 H, CH₂CH₃), 2.21-2.16 (m, 1 H, CH₂CH=CH₂), 2.14-2.08 (m, 1 H, CH₂CH=CH₂), 1.10 (s, 3 H, C(CH₃)₂), 1.07 (s, 3 H, C(CH₃)₂), 0.98 (t, J = 7.1 Hz, 3 H, CH₃CH₂), 0.87 (s, 9 H, SiC(CH₃)₃), 0.05 (s, 3 H, Si(CH₃)₂), 0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 215.9, 136.2, 116.5, 76.7, 52.9, 39.0, 31.9, 26.0, 22.4, 20.1, 18.2, 7.7, -3.6, -4.4.

Synthesis of Keto Aldehyde 87 as illustrated in Figure 12. Ozonolysis of Ketone 86. Alkene 86 (2.84 g, 10 mmol) was dissolved in Methylene chloride (25 mL) and the solution was cooled to -78 °C. Oxygen was bubbled through for 2 min after which time ozone was passed through until the reaction mixture adopted a blue color

(ca 30 min). The solution was then purged with oxygen for 2 min at -78 °C (disappearance of blue color) and Ph₃P (3.16 g, 12.0 mmol, 1.2 equiv) was added. The cooling bath was removed and the reaction mixture was allowed to reach room temperature and stirred for an additional 1 h. The solvent was removed, under reduced pressure and the mixture was purified by flash column chromatography (silica gel, 25% ether in hexanes) to provide pure keto aldehyde 87 (2.57 g, 90%): *R_f* = 0.45 (silica gel, 20% ether in hexanes); [α]_D²⁵ -1.9 (c 4.0, CHCl₃); IR (thin film) *n*_{max} 2935, 2858, 1707, 1467, 1388, 1255, 1093, 1004, 837, 777 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.78 (dd, *J* = 2.1, 2.0 Hz, CHO), 4.55 (dd, *J* = 6.0, 4.5 Hz, 1 H, CHOSi), 2.59-2.44 (m, 4 H, CH₂CH₃, CH₂CH=O), 1.13 (s, 3 H, C(CH₃)₂), 1.09 (s, 3 H, C(CH₃)₂), 1.00 (t, *J* = 7.0 Hz, 3 H, CH₃CH₂), 0.85 (s, 9 H, (CH₃)₃C), 0.06 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 215.3, 200.9, 71.3, 52.3, 48.5, 31.9, 25.8, 21.3, 20.4, 18.0, 7.5, -4.4, -4.9; FAB HRMS (NBA/NaI) *m/e* 309.1854, *M* + Na⁺ calcd for C₁₅H₃₀O₃Si 309.1862.

Synthesis of Keto Acid 76 as illustrated in Figure 12. Oxidation of Keto Aldehyde 87. Aldehyde 87 (2.86 g, 10 mmol), *t*BuOH (50 mL), isobutylene (20 mL, 2 M solution in THF, 40 mmol, 4.0 equiv), H₂O (10 mL), NaClO₂ (2.71 g, 30.0 mmol, 3.0 equiv) and NaH₂PO₄ (1.80 g, 15.0 mmol, 1.5 equiv) were combined and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was subjected to flash column

chromatography (silica gel, 50% ether in hexanes) to produce pure keto acid 76 (2.81 g, 93%). $R_f = 0.12$ (silica gel, 20% ether in hexanes); $[\alpha]_{22D} +16.1$ (c 1.0, CHCl₃); IR (thin film) ν_{max} 2934, 2858, 1710, 1467, 1254, 1093, 834 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 4.46 (dd, J = 7.0, 3.6 Hz, 1 H, CHOSi), 2.64-2.34 (m, 3 H, CH₂CH₃, CH₂COOH), 2.32 (q, J = 7.0 Hz, 1 H, CH₂CH₃), 1.13 (s, 3 H, C(CH₃)₂), 1.11 (s, 3 H, C(CH₃)₂), 0.99 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 0.83 (s, 9 H, (CH₃)₃C), 0.04 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 215.1, 178.2, 73.4, 52.4, 39.2, 31.6, 25.8, 20.8, 20.5, 18.0, 7.6, -4.5, -5.0; FAB HRMS (NBA) m/e 303.1996, M+ H⁺ calcd for C₁₅H₃₀O₃Si 303.1992.

Synthesis of Aldehyde 89 as illustrated in Figure 12. Reduction of Ester 88. Ethyl ester 88 (52.5 g, 0.306 mol; Aldrich) was dissolved in Methylene chloride (1 L) and cooled to -78 °C. DIBAL (490.0 mL, 1 M solution in Methylene chloride, 0.4896 mol, 1.6 equiv) was added dropwise via a cannula while the temperature of the reaction mixture was maintained at -78 °C. After the addition was complete, the reaction mixture was stirred at the same temperature until its completion was verified by TLC (ca 1 h). Methanol (100 mL) was added at -78 °C and was followed by addition of EtOAc (1 L) and saturated aqueous NH₄Cl solution (300 mL). The quenched reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 200 mL).

The combined organic phase was dried over MgSO_4 , filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 to 90% ether in hexanes) furnished the desired aldehyde 89 (33.6 g, 90%): R_f = 0.68 (silica gel, ether); IR (thin film) ν_{max} 3095, 2828, 1695, 1485, 1437, 1378, 1334, 1178, 1129, 1011 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.96 (s, 1 H, CHO), 8.0 (s, 1 H, SCH=C), 2.77 (s, 3 H, $\text{N}=\text{C}(\text{S})\text{CH}_3$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 184.2, 167.5, 154.8, 128.0, 19.1; FAB HRMS (NBA/NaI) m/e 149.9992, $M + \text{Na}^+$ calcd for $\text{C}_5\text{H}_5\text{NOS}$ 149.9990.

Synthesis of Aldehyde 90 as illustrated in Figure 12. Aromatic aldehyde 89 (31.1 g, 0.245 mol) was dissolved in benzene (500 mL) and 2-(triphenylphosphoranilidene)-propionaldehyde (90.0 g, 0.282 mol, 1.15 equiv) was added. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (ca 2 h). Evaporation of the solvent under reduced pressure, followed by flash column chromatography (10 to 90% ether in hexanes) produced the desired aldehyde 90 (40.08 g, 98%): R_f = 0.78 (silica gel, ether); IR (thin film) ν_{max} 3089, 1675, 1624, 1190, 1141, 1029, 947.6, 881 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.57 (s, 1 H, CHO), 7.46 (s, 1 H), 7.26 (s, 1 H), 2.77 (s, 3 H, $\text{N}=\text{C}(\text{S})\text{CH}_3$), 2.20 (s, 3 H, $\text{CH}=\text{C}(\text{CHO})\text{CH}_3$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 195.3, 165.7, 151.9, 140.9, 138.2, 122.6, 19.2, 10.9; FAB HRMS (NBA) m/e 168.0481, $M + \text{H}^+$ calcd for $\text{C}_8\text{H}_9\text{NOS}$ 168.0483.

Synthesis of Alcohol 91 as illustrated in Figure 12. Allylboration of Aldehyde 90. Aldehyde 90 (20.0 g, 0.120 mol) was dissolved in anhydrous ether (400 mL) and the solution was cooled to -100 °C. (+)-Diisopinocampheylallyl borane (1.5 equiv in pentane, prepared from 60.0 g of (-)-Ipc₂BOMe and 1.0 equiv of allyl magnesium bromide according to the method described for the synthesis of alcohol 85), was added dropwise under vigorous stirring, and the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol (40 mL) was added at -100 °C, and the reaction mixture was allowed to warm up to room temperature. Amino ethanol (72.43 mL, 1.2 mol, 10.0 equiv) was added and stirring was continued for 15 h. The work-up procedure was completed by the addition of saturated aqueous NH₄Cl solution (200 mL), extraction with EtOAc (4 x 100 mL) and drying of the combined organic layers with MgSO₄. Filtration, followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol 91 (24.09 g, 96%): R_f = 0.37 (60% ether in hexanes); [α]_D²⁰ -20.2 (c 1.0, CHCl₃); IR (thin film) ν_{max} 3357, 2923, 1642, 1505, 1437, 1322, 1186, 1018, 914, 878 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.81 (s, 1 H, SCH=C), 6.46 (s, 1 H, CH=CCH₃), 5.87-5.79 (m, 1 H, CH=CH₂), 5.02 (d, J = 17.1 Hz, 1 H, CH=CH₂), 4.97 (d, J = 10.3 Hz, 1 H, CH=CH₂), 4.12 (dd, J = 7.8, 5.0 Hz, 1 H,

CHOH), 3.8 (bs, 1 H, OH), 2.59 (s, 3 H, N=C(S)CH₃), 2.31 (dd, J = 7.0, 6.5 Hz, 2 H, CH₂=CHCH₂), 1.91 (s, 3 H, CH=CCH₃); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.5, 152.5, 141.8, 134.8, 118.7, 117.1, 115.1, 76.3, 39.8, 18.8, 14.1; FAB HRMS (NBA) m/e 210.0956, M + H⁺ calcd for C₁₁H₁₅NOS 210.0953.

Synthesis of Compound 92 as illustrated in Figure 12. Silylation of Alcohol 91. Alcohol 91 (7.0 g, 0.033 mol) was dissolved in DMF (35 mL, 1.0 M), the solution was cooled to 0 °C and imidazole (3.5 g, 0.050 mol, 1.5 equiv) was added. After stirring for 5 min, tert-butyltrimethylsilyl chloride (6.02 g, 0.040 mol, 1.2 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 45 min, and then at 25 °C for 2.5 h, after which time no starting alcohol was detected by TLC. Methanol (2 mL) was added at 0 °C and the solvent was removed under reduced pressure. Ether (100 mL) was added, followed by saturated aqueous NH₄Cl solution (20 mL), the organic phase was separated and the aqueous phase was extracted with ether (2 x 20 mL). The combined organic solution was dried (MgSO₄), filtered over celite and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 10 to 20% ether in hexanes) provided pure 92 (10.8 g, 99%): R_f = 0.70 (40% ether in hexanes); [α]_D²⁵ +1.39 (c 3.0, CHCl₃); IR (thin film) ν_{max} 2931, 2060, 1496, 1460, 1249, 1173, 1073, 908, 837, 779 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.80-5.75 (m, 1 H,

CH=CH₂), 5.03 (ddd, J = 17.1, 3.5, 1.5 Hz, 1 H, CH=CH₂),
 4.99 (ddd, J = 10.2, 2.1, 0.9 Hz, 1 H, CH=CH₂), 4.14 (dd,
 J = 6.6, 6.1 Hz, 1 H, CHOH), 2.69 (s, 3 H, N=C(S)CH₃),
 2.37-2.32 (m, 1 H, CH₂=CHCH₂), 2.31-2.25 (m, 1 H,
 5 CH₂=CHCH₂), 1.99 (s, 3 H, CH=CCH₃), 0.88 (s, 9 H,
 SiC(CH₃)₃), 0.05 (s, 3 H, Si(CH₃)₂), 0.00 (s, 3 H,
 Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 165.2, 153.9,
 142.9, 136.2, 119.7, 117.4, 115.9, 79.3, 42.1, 26.7, 20.1,
 19.0, 14.8, -3.8, -4.1; FAB HRMS (NBA) m/e 324.1804, M +
 10 H⁺ calcd for C₁₇H₂₉NOSSi 324.1817.

Synthesis of Aldehyde 82 as illustrated in Figure 12. Dihydroxylation of Olefin 92 and 1,2 Glycol Cleavage. Olefin 92 (16.7 g, 51.6 mmol) was dissolved in THF/tBuOH
 15 (1 : 1, 500 mL) and H₂O (50 mL). 4-Methylmorpholine N-oxide (NMO) (7.3 g, 61.9 mmol, 1.2 equiv) was added at 0 °C, followed by OsO₄ (5.2 mL, solution in tBuOH 1.0 mol%, 2.5% by weight). The mixture was vigorously stirred for 2.5 h at 0 °C and then for 12 h at 25 °C. After
 20 completion of the reaction, Na₂SO₃ (5.0 g) was added at 0 °C, followed by H₂O (100 mL). Stirring was continued for another 30 min and then ether (1 L) was added, followed by saturated aqueous NaCl solution (2 x 100 mL). The organic phase was separated and the aqueous phase was extracted
 25 with ether (2 x 100 mL). The combined organic extracts were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, ether to EtOAc) provided 17.54 g (95%) of the expected 1,2-diol as a 1:1 mixture of

diastereoisomers: $R_f = 0.55$ (silica gel, EtOAc); IR (thin film) ν_{\max} 3380, 2931, 2856, 1656, 1505, 1465, 1460, 1254, 1187, 1073, 908, 837, 777 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.90 and 6.88 (singlets, 1 H total, $\text{SCH}=\text{C}$), 6.52 and 6.47 (singlets, 1 H total, $\text{CH}=\text{CCH}_3$), 4.44-4.39 (m, 1 H), 3.95-3.84 (m, 1 H), 3.81-3.72 and 3.63-3.34 (m, 4 H total), 2.66 and 2.65 (singlets, 3 H total, $\text{N}=\text{C}(\text{S})\text{CH}_3$), 1.96 and 1.95 (singlets, 3 H total), 1.82-1.75 and 1.69-1.56 (m, 2 H total), 0.87 and 0.86 (singlets, 9 H total, $\text{SiC}(\text{CH}_3)_3$), 0.08 and -0.01 (singlets, 3 H total, $\text{Si}(\text{CH}_3)_2$), 0.07 and 0.10 (singlets, 3 H total, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 164.6, 164.5, 152.8, 152.4, 141.6, 141.5, 119.4, 118.4, 115.3, 115.2, 78.0, 75.4, 70.4, 68.8, 66.8, 66.5, 38.9, 38.7, 25.7, 19.0, 18.9, 18.0, 17.9, 14.6, 13.5, -4.6, -4.8, -5.2, -5.4; FAB HRMS (NBA/NaI) m/e 380.1699, $M + \text{Na}^+$ calcd for $\text{C}_{17}\text{H}_{31}\text{NO}_3\text{SSi}$ 380.1692.

The diol obtained from 92 as described above (5.2 g, 14.5 mmol) was dissolved in EtOAc (150 mL) and cooled to 0 °C. $\text{Pb}(\text{OAc})_4$ (8.1 g, 95% purity, 18.3 mmol, 1.2 equiv) was then added portionwise over 10 min, and the mixture was vigorously stirred for 15 min at 0 °C. After completion of the reaction, the mixture was filtered through silica gel and washed with 60% ether in hexanes. The solvents were then removed under reduced pressure providing pure aldehyde 82 (4.7 g, 98%): $R_f = 0.76$ (silica gel, 60% ether in hexanes); $[\alpha]_{\text{D}}^{25} -20.3$ (c 1.4, CHCl_3); IR (thin film) ν_{\max} 2931, 2856, 1726, 1504, 1466, 1389, 1254, 1182, 1087, 999, 839, 784 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.69 (dd, $J = 2.7, 2.2$ Hz, 1 H, CHO), 6.86 (s, 1 H, $\text{SCH}=\text{C}$), 6.48 (s,

1 H, CH=CCH₃), 4.60 (dd, J = 8.2, 3.9 Hz, 1 H, CHOSi),
 2.64 (ddd, J = 15.5, 8.3, 2.9 Hz, 1 H, CHOCH₂), 2.59 (s, 3
 H, N=C(S)CH₃), 2.41 (ddd, J = 15.5, 4.0, 2.0 Hz, 1 H,
 CHOCH₂), 1.95 (s, 3 H, CH=CCH₃), 0.79 (s, 9 H, SiC(CH₃)₃),
 0.00 (s, 3 H, Si(CH₃)₂), -0.06 (s, 3 H, Si(CH₃)₂); ¹³C NMR
 (125.7 MHz, CDCl₃) δ 201.0, 164.5, 152.4, 140.3, 119.0,
 115.8, 73.7, 49.9, 25.6, 18.9, 17.9, 13.9, -4.8, -5.4; FAB
 HRMS (NBA) m/e 326.1615, M + H⁺ calcd for C₁₆H₂₇NO₂SSi
 326.1610.

Synthesis of Alcohol 93 as illustrated in Figure
12. Reduction of Aldehyde 82. A solution of aldehyde 82
 (440 mg, 1.35 mmol) in MeOH (13 mL) was treated with NaBH₄
 (74 mg, 2.0 mmol, 1.5 equiv) at 0 °C for 15 min. The
 solution was diluted with ether (100 mL) and then
 saturated aqueous NH₄Cl solution (5 mL) was carefully
 added. The organic phase was washed with brine (10 mL),
 dried (MgSO₄) and concentrated. Flash column
 chromatography (silica gel, 60% ether in hexanes) gave
 alcohol 93 (425 mg, 96%) as a colorless oil. 26: R_f =
 0.52 (silica gel, 60% ether in hexanes); [α]_D²² -29.4 (c
 0.8, CHCl₃); IR (thin film) ν_{max} 3362, 2950, 2856, 1656,
 1505, 1466, 1362, 1254, 1186, 1075, 839, 777 cm⁻¹; ¹H NMR
 (500 MHz, CDCl₃) δ 6.86 (s, 1 H, SCH=C), 6.40 (s, 1 H,
 CH=CCH₃), 4.30 (dd, J = 7.6, 5.3 Hz, 1 H, CHOSi), 3.69-
 3.59 (m, 2 H, CH₂OH), 3.15 (s, 1 H, OH), 2.61 (s, 3 H,
 N=C(S)CH₃), 1.92 (s, 3 H, CH=CCH₃), 1.82-1.76 (m, 1 H,
 CH₂CH₂OH), 1.73-1.67 (m, 1 H, CH₂CH₂OH), 0.82 (s, 9 H,
 SiC(CH₃)₃), 0.02 (s, 3 H, Si(CH₃)₂), -0.05 (s, 3 H,

Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.3, 152.7, 141.6, 118.5, 115.1, 76.6, 59.6, 38.3, 25.8, 18.9, 18.0, 14.0, -4.8, -5.4; FAB HRMS (NBA/CsI) m/e 460.0727, M + Cs+ calcd for C₁₆H₂₉NO₂SSi 460.0743.

5

Synthesis of Iodide 94 as illustrated in Figure 12. Iodination of Alcohol 93. A solution of alcohol 93 (14.0 g, 42.7 mmol) in ether: MeCN (3:1, 250 mL) was cooled to 0 °C. Imidazole (8.7 g, 128.1 mmol, 3.0 equiv), Ph₃P (16.8 g, 64.1 mmol, 1.5 equiv), and iodine (16.3 g, 64.1 mmol, 1.5 equiv) were sequentially added and the mixture was stirred for 0.5 h at 0 °C. A saturated aqueous solution of Na₂S₂O₃ (50 mL) was added, followed by the addition of ether (600 mL). The organic phase was washed with brine (50 mL), dried (MgSO₄), and the solvents were removed under vacuum. Flash column chromatography (silica gel, 15% ether in hexanes) gave pure iodide 94 (16.6 g, 89%) as a colorless oil: R_f = 0.40 (silica gel, 10% ether in hexanes); [α]_D²⁵ +11.0 (c 1.0, CHCl₃); IR (thin film) ν_{max} 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.90 (s, 1 H, SCH=C), 6.53 (s, 1 H, CH=CCH₃), 4.19 (dd, J = 7.7, 4.5 Hz, 1 H, CHOSi), 3.18 (t, J = 7.3 Hz, 2 H, CH₂I), 2.67 (s, 3 H, N=C(S)CH₃), 2.10-2.05 (m, 1 H, CH₂CH₂I), 2.01-1.95 (m, 1 H, CH₂CH₂I), 1.99 (s, 3 H, CH=CCH₃), 0.87 (s, 9 H, SiC(CH₃)₃), 0.09 (s, 3 H, Si(CH₃)₂), 0.00 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.4, 152.7, 140.9, 119.3, 115.4, 78.0, 40.2, 25.8, 19.2, 18.1, 13.9, 3.1, -4.6, -5.0; FAB HRMS (NBA) m/e 438.0768, M + H+ calcd

25

for C₁₆H₂₈INOSSi 438.0784.

Synthesis of Phosphonium Salt 79 as illustrated in Figure 12.. A mixture of iodide 94 (16.5g, 37.7 mmol) and Ph₃P (10.9 g, 41.5 mmol, 1.1 equiv) was heated neat at 100 °C for 2 h. Purification by flash column chromatography (silica gel, Methylene chloride; then 7% MeOH in Methylene chloride) provided phosphonium salt 79 (25.9 g, 98%) as a white solid: R_f = 0.50 (silica gel, 7% MeOH in Methylene chloride); [α]_D²⁵ +3.7 (c 0.7, CHCl₃); IR (thin film) ν_{max} 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.78-7.28 (m, 15 H, aromatic), 6.97 (s, 1 H, SCH=C), 6.57 (s, 1 H, CH=CCH₃), 4.48 (dd, J = 6.3, 4.8 Hz, 1 H, CHOSi), 3.72-3.65 (m, 1 H, CH₂P), 3.31-3.25 (m, 1 H, CH₂P), 2.61 (s, 3 H, N=C(S)CH₃), 1.91 (s, 3 H, CH=CCH₃), 1.95-1.86 (m, 1 H, CH₂CH₂P), 1.82-1.74 (m, 1 H, CH₂CH₂ P), 0.83 (s, 9 H, SiC(CH₃)₃), 0.07 (s, 3 H, Si(CH₃)₂), -0.02 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.4, 152.3, 139.4, 135.1, 133.3, 133.2, 130.5, 130.4, 128.1, 119.8, 117.9, 117.3, 116.5, 76.0, 28.9, 25.7, 19.1, 18.4, 17.9, 14.5, -4.8.

Synthesis of Hydrazone 95 as illustrated in Figure 13. Alkylation of Hydrazone 80. Hydrazone 80 (20.0 g, 117.0 mmol, 1.0 equiv), dissolved in THF (80 mL), was added to a freshly prepared solution of LDA [19.75 mL of diisopropylamine (141.0 mmol, 1.2 equiv) was added to a solution of 88.1 mL of 1.6 M solution of n-BuLi in hexanes

(141 mmol, 1.2 equiv) in 160 mL of THF at 0 °C] at 0 °C. After stirring at this temperature for 8 h, the resulting yellow solution was cooled to -100 °C, and a solution of 4-iodo-1-benzyloxybutane (36.0 g, 124.0 mmol, 1.2 equiv) in THF (40 mL) was added dropwise over a period of 30 min. The mixture was allowed to warm to room temperature over 8 h, and was then poured into saturated aqueous NH₄Cl solution (40 mL) and extracted with ether (3 x 200 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated. Purification by flash column chromatography on silica gel (20% ether in hexanes) provided hydrazone 95 as a yellow oil (35.8 g, 92%, de > 98% by ¹H NMR): R_f = 0.45 (silica gel, 50% ether in hexanes); [α]_D²⁵ -55.0 (c 1.2, CHCl₃); IR (thin film) ν_{max} 2929, 2862, 1603, 1455, 1362, 1198, 1108, 737, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33 (s, 5 H, Ph), 6.48 (d, J = 6.5 Hz, 1 H, CH=NN), 4.46 (s, 2 H, CH₂Ph), 3.54 (dd, J = 9.0, 3.8 Hz, 1 H, CH₂OCH₃), 3.44 (t, J = 6.5 Hz, 2 H, CH₂OBn), 3.40 (dd, J = 9.0, 6.8 Hz, 1 H, CH₂OCH₃), 3.33 (s, 3 H, OCH₃), 2.65 (m, 1 H, CHCH₂OCH₃), 2.29 (m, 1 H, CH(CH₃)C=N), 1.94-1.76 (m, 4 H), 1.61 (m, 2 H), 1.45-1.36 (m, 6 H), 1.01 (d, J = 6.8 Hz, 3 H, CHCH₃); ¹³C NMR (125.7 MHz, CDCl₃) δ 144.6, 138.6, 128.2, 127.5, 127.3, 74.7, 72.7, 70.2, 63.4, 59.1, 50.4, 37.0, 35.2, 29.7, 26.4, 23.7, 22.0, 18.9; FAB HRMS (NBA) m/e 333.2552, M + H⁺ calcd for C₂₀H₃₂N₂O₂ 333.2542.

Synthesis of Aldehyde 96 as illustrated in Figure 13. Cleavage of Hydrazone 95. Procedure A: A solution

of hydrazone 95 (13.0 g, 39.1 mmol) in Methylene chloride (50 mL) was treated with ozone at -78 °C until the solution turned blue-green. The solution was purged with oxygen for 2 min at -78 °C, allowed to warm to room temperature, and then concentrated. The crude mixture so obtained was purified by flash column chromatography (silica gel, 10% ether in hexanes) to give aldehyde 96 (6.6 g, 77%) as a colorless oil. Procedure B: A solution of hydrazone 95 (30 g, 90.3 mmol) in MeI (100 mL) was heated at 60 °C. After 5 h, the reaction was complete (TLC), and the mixture was concentrated. The resulting crude product was suspended in n-pentane (360 mL) and was treated with 3 N aqueous HCl (360 mL). The two-phase system was vigorously stirred for 1 h, and the aqueous phase was extracted with n-pentane (3 x 200 mL). The combined organic solution was dried (MgSO₄), concentrated and purified by flash column chromatography (silica gel, 10% ether in hexanes) to give 96 (17.1 g, 86%): R_f = 0.49 (silica gel, 50% ether in hexanes); [α]_D²⁵ +11.6 (c 1.7, CHCl₃); IR (thin film) ν_{max} 2932, 2856, 1715, 1450, 1361, 1272, 1202, 1102, 920, 732, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.60 (d, J = 2.0 Hz, 1 H, CHO), 7.34 (s, 5 H, Ph), 4.50 (s, 2 H, CH₂Ph), 3.47 (t, J = 6.5 Hz, 2 H, CH₂OBn), 2.33 (m, 1 H, CH(CH₃)CO), 1.75-1.69 (m, 1 H), 1.65-1.61 (m, 2 H), 1.49-1.34 (m, 3 H), 1.08 (d, J = 7.0 Hz, 3 H, CHCH₃); ¹³C NMR (125.7 MHz, CDCl₃) δ 205.0, 138.4, 128.2, 127.5, 127.4, 72.8, 69.9, 46.1, 30.1, 29.6, 23.6, 13.2; FAB HRMS (NBA) m/e 221.1538, M + H⁺ calcd for C₁₄H₂₀O₂ 221.1542.

Synthesis of Alcohol 97 as illustrated in Figure 13: Reduction of Aldehyde 96. A solution of aldehyde 96 (17.0 g, 77.0 mmol) in MeOH (200 mL) was treated with NaBH₄ (8.6 g, 228 mmol, 3.0 equiv) at 0 °C for 15 min. The solution was then diluted with ether (400 mL) and saturated aqueous NH₄Cl solution (50 mL) was carefully added. The organic phase was washed with brine (50 mL), dried (MgSO₄), and concentrated. The crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol 97 (16.8 g, 98%) as a colorless oil: R_f = 0.23 (silica gel, 50% ether in hexanes); [α]_D²⁵ -5.1 (c 1.9, CHCl₃); IR (thin film) ν_{max} 3401, 2931, 2860, 1455, 1361, 1267, 1202, 1102, 1037, 937, 732, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH₂Ph), 3.50 (dd, J = 11.0, 6.0 Hz, 1 H, CH₂OH), 3.48 (t, J = 6.5 Hz, 2 H, CH₂OBn), 3.42 (dd, J = 11.0, 6.5 Hz, 1 H, CH₂OH), 1.65-1.59 (m, 2 H), 1.47-1.34 (m, 4 H), 1.15-1.12 (m, 1 H), 0.91 (d, J = 6.7 Hz, 3 H, CHCH₃); ¹³C NMR (125.7 MHz, CDCl₃) δ 138.6, 128.2, 127.6, 127.3, 72.9, 70.3, 68.1, 35.7, 32.9, 30.1, 23.6, 14.1; FAB HRMS (NBA) m/e 223.1705, M + H⁺ calcd for C₁₄H₂₂O₂ 223.1698.

Synthesis of Silyl Ether 98 as illustrated in Figure 13. Silylation of Alcohol 97. Alcohol 97 (17.0 g, 76.0 mmol) was dissolved in Methylene chloride (350 mL), the solution was cooled to 0 °C and Et₃N (21.2 mL, 152.0 mmol, 2.0 equiv) and 4-DMAP (185 mg, 1.52 mmol, 0.05

equiv) were added. After stirring for 5 min, tert-butyldimethylsilyl chloride (17.3 g, 115 mmol, 1.5 equiv) was added portionwise, and the reaction mixture was allowed to stir at 0 °C for 2 h, and then at 25 °C for 10 h. Methanol (20 mL) was added at 0 °C and the solvents were removed under reduced pressure. Ether (200 mL) and saturated aqueous NH₄Cl solution (30 mL) were sequentially added, and the organic phase was separated. The aqueous phase was extracted with ether (2 x 100 mL) and the combined organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure silyl ether 98 (24.4 g, 95%): R_f = 0.54 (silica gel, 10% ether in hexanes); [α]_D²⁵ -2.3 (c 1.1, CHCl₃); IR (thin film) ν_{max} 2931, 2860, 1461, 1361, 1249, 1091, 839, 773, 738 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH₂Ph), 3.48 (t, J = 6.5 Hz, 2 H, CH₂OBn), 3.43 (dd, J = 10.5, 6.0 Hz, 1 H, CH₂OSi), 3.36 (dd, J = 10.5, 6.5 Hz, 1 H, CH₂OSi), 1.64-1.60 (m, 3 H), 1.47-1.29 (m, 3 H), 1.15-1.05 (m, 1 H), 0.90 (s, 9 H, SiC(CH₃)₃), 0.87 (d, J = 6.8 Hz, 3 H, CHCH₃), 0.043 (s, 3 H, Si(CH₃)₂), 0.041 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 138.6, 128.2, 127.5, 127.3, 72.7, 70.3, 68.3, 35.6, 32.9, 30.0, 25.8, 23.5, 18.1, 16.6, -5.5; FAB HRMS (NBA) m/e 337.2553, M + H⁺ calcd for C₂₀H₃₆O₂Si 337.2563.

Synthesis of Alcohol 99 as illustrated in Figure 13. Hydrogenolysis of Benzyl Ether 98. To a solution of

benzyl ether 98 (21.0 g, 62.5 mmol) in THF (200 mL) was added 10% Pd(OH)2/C (1.0 g). The reaction was allowed to proceed under an atmosphere of H2 at a pressure of 50 psi and at 25 °C (Parr hydrogenator apparatus). After 15 min, no starting benzyl ether was detected by TLC, and the mixture was filtered through celite. The clear solution was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol 99 (14.7 g, 95%) as a colorless oil: R_f = 0.32 (silica gel, 50% ether in hexanes); $[\alpha]_D^{25}$ -3.6 (c 3.6, CHCl3); IR (thin film) ν_{max} 3342, 2931, 2860, 1467, 1384, 1249, 1085, 838, 773, 667 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 3.63 (t, J = 7.0 Hz, 2 H, CH2OH), 3.42 (dd, J = 11.0, 6.0 Hz, 1 H, CH2OSi), 3.35 (dd, J = 11.0, 7.0 Hz, 1 H, CH2OSi), 1.57-1.53 (m, 3 H), 1.42-1.39 (m, 3 H), 1.16-1.06 (m, 1 H), 0.88 (s, 9 H, Si(CH3)3), 0.85 (d, J = 6.5 Hz, 3 H, CHCH3), 0.03 (s, 3 H, Si(CH3)2), 0.02 (s, 3 H, Si(CH3)2); ¹³C NMR (125.7 MHz, CDCl3) δ 68.2, 62.7, 35.6, 32.9, 32.8, 25.7, 23.0, 18.2, 16.5, -5.5; FAB HRMS (NBA) m/e 247.2097, $M + H^+$ calcd for C13H30O2Si 247.2093.

Synthesis of Aldehyde 77 as illustrated in Figure 13. Oxidation of Alcohol 99. To a solution of oxalyl chloride (5.6 mL, 65.0 mmol, 2.0 equiv) in Methylene chloride (250 mL) was added dropwise DMSO (9.2 mL, 130 mmol, 4.0 equiv) at -78 °C. After stirring for 15 min, a solution of alcohol 99 (8.0 g, 32.0 mmol, 1.0 equiv) in Methylene chloride (50 mL) was added dropwise at -78 °C

over a 15 min period. The solution was stirred for further 30 min at -78 °C, and Et₃N (27.1 mL, 194 mmol, 6.0 equiv) was added at the same temperature. The reaction mixture was allowed to warm to 0 °C over 30 min and then ether (400 mL) was added, followed by saturated aqueous NH₄Cl solution (100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 x 300 mL). The combined organic solution was dried (MgSO₄), filtered and concentrated under reduced pressure.

Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde 77 (7.9 g, 98%) as a colorless oil: R_f = 0.64 (silica gel, 50% ether in hexanes); [α]_D²⁵ -5.1 (c 0.7, CHCl₃); IR (thin film) ν_{max} 2952, 2858, 1728, 1466, 1389, 1254, 1095, 841, 776 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.74 (t, J = 1.5 Hz, 1 H, CHO), 3.39 (dd, J = 9.8, 6.1 Hz, 1 H, CH₂OSi), 3.36 (dd, J = 9.8, 6.3 Hz, 1 H, CH₂OSi), 2.39 (m, 2 H, CH₂CHO), 1.71-1.64 (m, 1 H), 1.61-1.53 (m, 2 H), 1.44-1.38 (m, 1 H), 1.11-1.05 (m, 1 H), 0.87 (s, 9 H, Si(CH₃)₃), 0.85 (d, J = 6.5 Hz, 3 H, CHCH₃), 0.019 (s, 3 H, Si(CH₃)₂), 0.004 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 202.7, 68.9, 44.1, 35.5, 32.6, 25.8, 23.0, 18.2, 16.5, -5.5; FAB HRMS (NBA) m/e 245.1932, M + H⁺ calcd for C₁₃H₂₈O₂Si 245.1937.

Synthesis of Alcohol 100 as illustrated in Figure 13. To a cold (0 °C) solution of aldehyde 77 (7.8 g, 32.0 mmol) in THF (300 mL) was slowly added MeMgBr (1.0 M solution in THF, 48.0 mL, 48.0 mmol, 1.5 equiv). The

reaction mixture was stirred for 15 min at 0 °C and then it was diluted with ether (500 mL) and quenched by careful addition of saturated aqueous NH₄Cl solution (100 mL). The organic phase was washed with brine (100 mL), dried (MgSO₄), and concentrated. The crude product so obtained was purified by flash column chromatography (silica gel, 30% ether in hexanes) to give alcohol 100 (7.0 g, 84%) as a colorless oil: R_f = 0.38 (silica gel, 50% ether in hexanes); IR (thin film) ν_{max} 3352, 2931, 2858, 1465, 1384, 1253, 1096, 839, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.79 (m, 1 H, CH(CH₃)OH), 3.43 (dd, J = 9.8, 6.0 Hz, 1 H, CH₂OSi), 3.36 (dd, J = 9.8, 6.8 Hz, 1 H, CH₂OSi), 1.61-1.57 (m, 1 H), 1.47-1.35 (m, 4 H), 1.30-1.26 (m, 1 H), 1.19 (d, J = 6.1 Hz, 3 H, CH(OH)CH₃), 1.09-1.05 (m, 1 H), 0.89 (s, 9 H, Si(CH₃)₃), 0.86 (d, J = 6.7 Hz, 3 H, CHCH₃), 0.04 (s, 6 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 68.2, 67.9, 39.5, 35.6, 33.0, 25.9, 23.4, 23.1, 18.2, 16.6, -5.4; FAB HRMS (NBA) m/e 261.2256, M + H⁺ calcd for C₁₄H₃₂O₂Si 261.2250.

Synthesis of Ketone 78 as illustrated in Figure 13.
Oxidation of Alcohol 100. To a solution of alcohol 100 (7.0 g, 27.0 mmol) in Methylene chloride (250 mL) was added molecular sieves (4 Å, 6.0 g) 4-methylmorpholine-N-oxide (NMO) (4.73 g, 40.0 mmol, 1.5 equiv) and tetrapropylammonium perruthenate (TPAP) (189 mg, 0.54 mmol, 0.02 equiv) at room temperature. After stirring for 45 min (depletion of starting material, TLC), the reaction mixture was filtered through celite, and the solvent was

removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% ether in hexanes) to give ketone 78 (6.6 g, 96%) as a colorless oil: $R_f = 0.67$ (silica gel, 50% ether in hexanes); $[\alpha]_{22D} -4.5$ (c 1.1, $CHCl_3$); IR (thin film) ν_{max} 2931, 2849, 1713, 1461, 1355, 1249, 1161, 1091, 838, 773, 667 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 3.41 (dd, $J = 9.8$, 6.0 Hz, 1 H, CH_2OSi), 3.36 (dd, $J = 9.8$, 6.3 Hz, 1 H, CH_2OSi), 2.41 (m, 2 H, CH_2COCH_3), 2.13 (s, 3 H, $COCH_3$), 1.68-1.48 (m, 3 H), 1.42-1.35 (m, 1 H), 1.09-1.00 (m, 1 H), 0.88 (s, 9 H, $Si(CH_3)_3$), 0.86 (d, $J = 6.7$ Hz, 3 H, $CHCH_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 209.8, 68.0, 43.9, 35.5, 32.6, 29.7, 25.8, 21.2, 18.2, 16.4, -5.5; FAB HRMS (NBA) m/e 259.2097, $M + H^+$ calcd for $C_{14}H_{30}O_2Si$ 259.2093.

Synthesis of Iodide 113 as illustrated in Figure 15. Iodination of Alcohol 99. A solution of alcohol 99 (3.8 g, 15.0 mmol) in ether:MeCN 3:1 (150 mL) was cooled to 0 °C. Imidazole (3.1 g, 45.0 mmol, 3.0 equiv), Ph_3P (5.9 g, 22.5 mmol, 1.5 equiv) and iodine (5.7 g, 22.5 mmol, 1.5 equiv) were sequentially added and the reaction mixture was stirred at 0 °C for 0.5 h. A saturated aqueous solution of $Na_2S_2O_3$ (200 mL) was added followed with ether (200 mL). The organic phase was washed with brine (200 mL), dried ($MgSO_4$) and the solvents were removed under vacuum. The crude product was purified by flash column chromatography (silica gel, 10% ether in hexanes) to give pure iodide 113 (4.9 g, 91%) as a

colorless oil: R_f = 0.68 (silica gel, 10% ether in hexanes); $[\alpha]_{22D}$ -4.3 (c 1.2, $CHCl_3$); IR (thin film) ν_{max} 2929, 2860, 1461, 1386, 1248, 1090, 836, 774, 664 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 3.42 (dd, J = 10.0, 6.5 Hz, 1 H, CH_2OSi), 3.38 (dd, J = 10.0, 6.0 Hz, 1 H, CH_2OSi), 3.19 (t, J = 7.0 Hz, 2 H, CH_2I), 1.85-1.78 (m, 2 H), 1.61-1.55 (m, 1 H), 1.47-1.33 (m, 3 H), 1.10-1.02 (m, 1 H, CH_2), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.87 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 68.1, 35.4, 33.7, 31.8, 27.8, 25.8, 18.2, 16.5, 7.1, -5.5; FAB HRMS (NBA) m/e 229.1983, $M - I$ - calcd for $C_{13}H_{39}IOSi$ 229.1988.

Synthesis of Phosphonium Salt 114 as illustrated in Figure 15. A mixture of iodide 113 (4.7 g, 13.1 mmol) and Ph_3P (3.8 g, 14.4 mmol, 1.1 equiv) was heated neat at 100 °C for 2 h. Purification by flash column chromatography (silica gel, Methylene chloride to 7% MeOH in Methylene chloride) provided phosphonium salt 114 (7.4 g, 91%) as a white solid: R_f = 0.42 (silica gel, 5% MeOH in Methylene chloride); $[\alpha]_{22D}$ -7.3 (c 1.5, $CHCl_3$); IR (thin film) ν_{max} 2931, 2849, 1578, 1461, 1431, 1243, 1184, 1102, 997, 914, 838, 720, 685, 532, 503 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.82-7.77 (m, 9 H, Ph), 7.74-7.68 (m, 6 H, Ph), 3.62 (dt, J = 12.5, 8.0 Hz, 2 H, CH_2P), 3.34 (dd, J = 9.5, 6.5 Hz, 1 H, CH_2OSi), 3.30 (dd, J = 9.5, 6.5 Hz, 1 H, CH_2OSi), 1.69-1.55 (m, 4 H), 1.50-1.46 (m, 1 H), 1.39-1.32 (m, 1 H), 1.10-1.01 (m, 1 H), 0.83 (s, 9 H, $SiC(CH_3)_3$), 0.79 (d, J = 6.6 Hz, 3 H, $CHCH_3$), -0.04 (s, 6 H,

Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 135.0, 133.6, 133.5, 133.2, 130.5, 130.4, 68.0, 35.2, 32.4, 27.8, 25.8, 23.2, 22.7, 18.2, 16.4, -5.5.

5 **Synthesis of Olefin 101 as illustrated in Figure**
15. Method A. From Phosphonium Salt 79 and Aldehyde 77. Phosphonium salt 79 (13.60 g, 19.4 mmol, 1.2 equiv) was dissolved in THF (80 mL, 0.2 M) and the solution was cooled to 0 °C. Sodium hexamethyldisilylamide (NaHMDS, 10 19.4 mL, 19.4 mmol, 1.0 M solution in THF, 1.2 equiv) was slowly added and the resulting mixture was stirred for 15 min before aldehyde 77 (3.96 g, 16.2 mmol, 1.0 equiv, in 10 mL of THF) was added at the same temperature. Stirring was continued for another 15 min at 0 °C and then, the 15 reaction mixture was quenched with saturated aqueous NH₄Cl solution (25 mL). Ether (250 mL) was added and the organic phase was separated and washed with brine (2 x 40 mL), dried (MgSO₄) and concentrated under vacuo. The crude product was purified by flash column chromatography 20 (silica gel, 10% ether in hexane) to afford olefin 34 (6.70 g, 77%) as a mixture of Z- and E-isomers (ca 9 : 1 by ¹H NMR). Method B. From Phosphonium Salt 114 and Aldehyde 82. Phosphonium salt 114 (7.40 g, 11.96 mmol, 1.2 equiv) was dissolved in THF (120 mL, 0.1 M) and the 25 solution was cooled to 0 °C. Sodium hexamethyldisilylamide (NaHMDS, 11.96 mL, 11.96 mmol, 1.0 M solution in THF, 1.2 equiv) was slowly added at the same temperature and the resulting mixture was stirred for 15 min, before aldehyde 82 (3.20 g, 9.83 mmol, 1.0 equiv, in

20 mL of THF; *vide supra*) was slowly added. Stirring was continued for another 15 min at 0 °C and then the mixture was quenched with saturated aqueous NH₄Cl solution (150 mL). Ether (200 mL) was added and the organic phase was separated and washed with brine (2 x 150 mL), dried (MgSO₄) and concentrated under reduced pressure to afford the crude product. Flash column chromatography (silica gel, 10% ether in hexane) furnished olefin 101 (3.65 g, 69% yield) as a mixture of Z- and E-isomers (ca 9:1 by ¹H NMR): R_f = 0.75 (silica gel, 50% ether in hexane); [α]_D²² +4.0 (c 0.5, CHCl₃); IR (thin film) ν_{max} 2930, 2856, 1465, 1388, 1253, 1089, 939, 838 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (signals for the Z-isomer (34) only reported) δ 6.92 (s, 1 H, SCH=C), 6.46 (s, 1 H, CH=CCH₃), 5.49-5.31 (m, 2 H, CH=CH), 4.12 (dd, J = 6.5, 6.4 Hz, 1 H, CHOSi), 3.44 (dd, J = 9.8, 5.8 Hz, 1 H, CH₂OSi), 3.34 (dd, J = 9.8, 6.8 Hz, 1 H, CH₂OSi), 2.71 (s, 3 H, N=C(S)CH₃), 2.39-2.24 (m, 2 H, CH₂CHOSi), 2.00 (s, 3 H, CH=CCH₃), 2.05-1.96 (m, 2 H), 1.59-1.51 (m, 1 H), 1.42-1.23 (m, 3 H), 1.10-0.98 (m, 1 H), 0.89 (s, 18 H, SiC(CH₃)₃), 0.85 (d, J = 6.8 Hz, 3 H, CH₃CH), 0.06 (s, 3 H, Si(CH₃)₂), 0.04 (s, 6 H, Si(CH₃)₂), 0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.3, 153.1, 142.2, 131.4, 125.7, 118.8, 114.9, 78.7, 68.3, 35.7, 34.6, 32.9, 27.8, 27.1, 25.9, 25.8, 19.2, 18.3, 18.2, 16.7, 13.9, -4.7, -4.9, -5.4; FAB HRMS (NBA) m/e 538.3582, M + H⁺ calcd for C₂₉H₅₅NO₂SSi₂ 538.3570.

Synthesis of alcohol 102 as illustrated in Figure 14. Compound 101 (1.77 g, 3.29 mmol) was dissolved in

Methylene chloride : MeOH (1:1, 66 mL) and the solution
 was cooled to 0 °C and CSA (764 mg, 3.29 mmol, 1.0 equiv) *
 was added over a 5 min period. The mixture was stirred
 for 30 min at 0 °C, and then for 1 h at 25 °C. Et3N (2.0
 5 mL) was added, and the solvents were removed under reduced
 pressure. Flash column chromatography (silica gel, 50%
 ether in hexanes) furnished the desired alcohol 35 (1.2 g,
 86%): Rf = 0.72 (silica gel, 80% ether in hexanes); [α]_D²⁵
 +1.1 (c 1.0, CHCl₃); IR (thin film) ν_{max} 3370, 2923, 2857,
 10 1464, 1384, 1253, 1185, 1074, 836, 776 cm⁻¹; ¹H NMR (500
 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H,
 CH=CCH₃), 5.45-5.32 (m, 2 H, CH=CH), 4.12 (dd, J = 6.5,
 6.4 Hz, 1 H, CHOSi), 3.46 (dd, J = 10.5, 5.9 Hz, 1 H,
 CH₂OH), 3.37 (dd, J = 10.5, 6.5 Hz, 1 H, CH₂OH), 2.68 (s,
 15 3 H, N=C(S)CH₃), 2.39-2.21 (m, 2 H, CH₂CHOSi), 2.21 (s, 1
 H, OH), 1.98 (s, 3 H, CH=CCH₃), 2.05-1.95 (m, 2 H), 1.59-
 1.51 (m, 1 H), 1.42-1.23 (m, 3 H), 1.10-0.98 (m, 1 H),
 0.88 (d, J = 6.5 Hz, 3 H, CH₃CH), 0.87 (s, 9 H,
 SiC(CH₃)₃), 0.05 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H,
 20 Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 164.4, 152.9,
 142.2, 131.2, 125.8, 118.7, 114.8, 78.6, 67.9, 35.5, 34.6,
 32.7, 27.5, 26.9, 25.8, 25.7, 18.9, 16.5, 13.7, -4.8, -
 5.1; FAB HRMS (NBA/NaI) m/e 446.2534, M + Na⁺ calcd for
 C₂₃H₄₁NO₂SSi 446.2525.

25 **Synthesis of Aldehyde 74 as illustrated in Figure**
14. Oxidation of Alcohol 102. Alcohol 102 (1.9 g, 4.5
 mmol) was dissolved in Methylene chloride (45 mL, 0.1 M).
 DMSO (13.5 mL), Et₃N (3.0 mL, 22.4 mmol, 5.0 equiv) and

SO₃·pyr (1.43 g, 8.98 mmol, 2.0 equiv) were added at 25 °C and the resulting mixture was stirred for 30 min. Saturated aqueous NH₄Cl solution (100 mL) and ether (200 mL) were added sequentially. The organic phase was washed with brine (2 x 30 mL), dried (MgSO₄) and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 30% ether in hexanes) furnished aldehyde 74 (1.79 g, 94%): R_f = 0.55 (silica gel, 40% ether in hexanes); [α]_D²⁵ +13.3 (c 0.7, CHCl₃); IR (thin film) ν_{max} 2930, 2856, 1725, 1504, 1462, 1385, 1253, 1182, 1076, 938, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.57, (d, J = 1.8 Hz, 1 H, CHO), 6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H, CH=CCH₃), 5.45-5.35 (m, 2 H, CH=CH), 4.11 (dd, J = 6.6, 6.3 Hz, 1 H, CHOSi), 2.69 (s, 3 H, N=C(S)CH₃), 2.34-2.24 (m, 3 H), 2.05-2.01 (m, 2 H), 1.98 (s, 3 H, CH=CCH₃), 1.71-1.64 (m, 1 H), 1.41-1.29 (m, 3 H), 1.05 (d, J = 7.0 Hz, 3 H, CH₃CH), 0.87 (s, 9 H, SiC(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 205.2, 164.4, 153.0, 142.0, 130.6, 126.4, 118.8, 115.0, 78.7, 46.2, 34.7, 30.0, 27.3, 26.9, 25.8, 19.2, 18.2, 13.9, 13.2, -4.7, -5.0; FAB HRMS (NBA) m/e 422.2559, M + H⁺ calcd for C₂₃H₃₉NO₂SSi 422.2549.

Synthesis of compounds 105 and 106 as illustrated in Figure 14: Aldol Reaction of Keto Acid 76 with Aldehyde 74. A solution of keto acid 76 (1.52 g, 5.10 mmol, 1.2 equiv; synthesized *vide supra*) in THF (10 mL) was added dropwise to a freshly prepared solution of LDA

[diisopropylamine (1.78 mL, 12.78 mmol) was added to n-BuLi (7.95 mL, 1.6 M solution in hexanes, 12.78 mmol) in 20 mL of THF at 0 °C] at -78 °C. After stirring for 15 min, the solution was allowed to warm to -40 °C, and after 5 0.5 h at that temperature it was recooled to -78 °C. A solution of aldehyde 74 (1.79 g, 4.24 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred for 15 min, and then quenched at -78 °C by slow addition of saturated aqueous NH₄Cl solution (20 mL). The reaction 10 mixture was warmed to 0 °C, and AcOH (2.03 mL, 26.84 mmol, 6.3 equiv) was added, followed by addition of EtOAc (50 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic solution was dried over MgSO₄ and concentrated 15 under vacuum to afford a mixture of aldol products 103a:103b in a ca 1:1 ratio (1H NMR) and unreacted keto acid 76. The mixture was dissolved in Methylene chloride (50 mL) and treated, at 0 °C, with 2,6-lutidine (3.2 mL, 27.36 mmol) and tert-butyldimethylsilyl 20 trifluoromethanesulfonate (4.2 mL, 18.24 mmol). After stirring for 2 h (complete reaction by TLC), aqueous HCl (20 mL, 10% solution) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with Methylene chloride (3 x 20 mL) and the combined 25 organic solution was washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure to give a mixture of the tetra-tert-butyldimethylsilyl ethers 104a and 104b. The crude product was dissolved in MeOH (50 mL) and K₂CO₃ (1.40 g, 10.20 mmol) was added at 25 °C. The

reaction mixture was vigorously stirred for 15 min, and
 then filtered. The residue was washed with MeOH (20 mL)
 and the solution was acidified with ion exchange resin
 (DOWEX 50WX8-200) to pH 4-5, and filtered again. The
 solvent was removed under reduced pressure and the
 resulting residue was dissolved in EtOAc (50 mL) and
 washed with saturated aqueous NH_4Cl solution (50 mL). The
 aqueous phase was extracted with EtOAc (4 x 25 mL) and the
 combined organic solution was dried (MgSO_4), filtered and
 concentrated to furnish a mixture of carboxylic acids 105,
 106 and 76. Purification by preparative thin layer
 chromatography (silica gel, 5% MeOH in Methylene
 chloride), gave pure acids 105 (1.1 g, 31% from 7) and 106
 (1.0 g, 30% from 7) as colorless oils. 38: $R_f = 0.61$
 (silica gel, 5% MeOH in Methylene chloride); $[\alpha]_{22D} -8.8$
 (c 0.8, CHCl_3); IR (thin film) ν_{max} 2931, 2856, 1712,
 1466, 1254, 1083, 836 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ
 6.94 (s, 1 H, $\text{SCH}=\text{C}$), 6.61 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.44-5.41
 (m, 2 H, $\text{CH}=\text{CH}$), 4.40 (dd, $J = 6.5, 3.2$ Hz, 1 H,
 $(\text{CH}_3)_2\text{CCHOSi}$), 4.11 (dd, $J = 6.5, 5.9$ Hz, 1 H,
 CH_2CHOSi), 3.75 (dd, $J = 6.5, 3.0$ Hz, 1 H, $\text{CH}(\text{CH}_3)\text{CHOSi}$),
 3.12 (dq, $J = 7.0, 6.5$ Hz, 1 H, $\text{C}(\text{O})\text{CH}(\text{CH}_3)$), 2.69 (s, 3
 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.48 (dd, $J = 16.0, 3.2$ Hz, 1 H, CH_2COOH),
 2.35 (dd, $J = 16.0, 6.7$ Hz, 1 H, CH_2COOH), 2.39-2.28 (m, 2
 H, $\text{CH}_2\text{CH}=\text{CH}$), 2.10-1.92 (m, 2 H, $\text{CH}=\text{CHCH}_2$), 1.95 (s, 3 H,
 $\text{CH}=\text{C}(\text{CH}_3)$), 1.42-1.30 (m, 5 H, $\text{CH}(\text{CH}_3)$, 2 x CH_2), 1.18 (s,
 3 H, $\text{C}(\text{CH}_3)_2$), 1.10 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.06 (d, $J = 7.0$
 Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.90-0.85 (m, 30 H, $\text{CH}(\text{CH}_3)$, 3 x
 $\text{SiC}(\text{CH}_3)_3$), 0.12 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.09 (s, 3 H,

Si(CH₃)₂, 0.07 (s, 3 H, Si(CH₃)₂), 0.05 (s, 3 H,
 Si(CH₃)₂), 0.04 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H,
 Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 218.1, 176.7,
 164.8, 152.8, 142.6, 131.3, 125.9, 118.6, 114.7, 78.6,
 5 77.4, 73.4, 53.5, 44.9, 40.1, 38.8, 34.6, 30.7, 28.0,
 27.8, 26.2, 26.0, 25.8, 23.6, 19.1, 18.8, 18.5, 18.2,
 17.4, 15.7, 13.8, -3.7, -3.8, -4.2, -4.6, -4.7, -4.9; FAB
 HRMS (NBA/CsI) m/e 970.4318, M + Cs⁺ calcd for
 C₄₄H₈₃NO₆SSi₃ 970.4303. 39: R_f = 0.70 (silica gel, 5%
 10 MeOH in Methylene chloride); [α]_D²² +2.2 (c 3.5, CHCl₃);
 IR (thin film) ν_{max} 2929, 2856, 1713, 1470, 1386, 1254,
 1082, 988, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.91
 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.44-5.38 (m, 1
 H, CH=CH), 5.37-5.32 (m, 1 H, CH=CH), 4.55 (dd, J = 6.7,
 15 3.7 Hz, 1 H, (CH₃)₂CCHOSi), 4.11 (dd, J = 6.7, 6.2 Hz, 1
 H, CH₂CHOSi), 3.83 (d, J = 8.4, 1 H, CH(CH₃)CHOSi), 3.09
 (dq, J = 7.0, 6.9 Hz, 1 H, C(O)CH(CH₃)), 2.73 (s, 3 H,
 N=C(CH₃)S), 2.40 (dd, J = 16.3, 3.8 Hz, 1 H, CH₂COOH),
 2.35-2.22 (m, 3 H, CH₂COOH, CH₂CH=CH), 1.98-1.94 (m, 2 H,
 20 CH=CHCH₂), 1.92 (s, 3 H, CH=C(CH₃)), 1.34-1.21 (m, 5 H,
 CH(CH₃), 2 x CH₂), 1.18 (s, 3 H, C(CH₃)₂), 1.07 (s, 3 H,
 C(CH₃)₂), 1.05 (d, J = 7.0 Hz, 3 H, CH(CH₃)), 0.89 (s, 9
 H, SiC(CH₃)₃), 0.88 (s, 9 H, SiC(CH₃)₃), 0.85 (s, 9 H,
 SiC(CH₃)₃), 0.82 (d, J = 6.9 Hz, 3 H, CH(CH₃)), 0.07 (s, 6
 25 H, 2 x Si(CH₃)₂), 0.06 (s, 3 H, Si(CH₃)₂), 0.05 (s, 3 H,
 Si(CH₃)₂), 0.04 (s, 3 H, Si(CH₃)₂), 0.01 (s, 3 H,
 Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 217.7, 175.3,
 165.4, 152.4, 143.1, 131.3, 125.9, 118.3, 114.6, 78.6,
 76.7, 72.3, 53.8, 45.7, 40.1, 37.9, 34.9, 34.6, 27.7,

27.3, 26.3, 26.2, 26.0, 25.8, 22.4, 19.0, 18.6, 18.2, 18.1, 16.8, 13.9, 13.5, -3.4, -3.6, -4.3, -4.6, -4.7, -4.9; FAB HRMS (NBA/CsI) m/e 970.4331, M + Cs+ calcd for C₄₄H₈₃NO₆SSi₃ 970.4303.

5

10

15

20

25

Synthesis of Hydroxy Acid 72 as illustrated in Figure 14. Selective Desilylation of tris(Silyl) Ether 105. A solution of tris(silyl) ether 105 (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (10 mL), dried (MgSO₄) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in Methylene chloride) to provide hydroxy acid 72 (203 mg, 78%) as a yellow oil: R_f = 0.40 (silica gel, 5% MeOH in Methylene chloride); [α]_D²⁵ -19.2 (c 0.1, CHCl₃); IR (thin film) ν_{max} 3358, 2932, 2857, 1701, 1466, 1254, 1088, 988, 835 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.95 (s, 1 H SCH=C), 6.67 (s, 1 H, CH=CCH₃), 5.58-5.54 (m, 1 H, CH=CH), 5.43-5.39 (m, 1 H, CH=CH), 4.39 (dd, J = 6.7, 3.9 Hz, 1 H, (CH₃)₂CCHOSi), 4.18 (dd, J = 7.5, 5.0 Hz, 1 H, CH₂CHOH), 3.78 (dd, J = 6.9, 1.0 Hz, 1 H, CH(CH₃)CHOSi), 3.11 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)CHCH₃), 2.70 (s, 3 H, N=C(CH₃)S), 2.43 (dd, J = 16.2, 3.9 Hz, 1 H, CH₂COOH), 2.40-2.35 (m, 2 H, CH₂CH=CH), 2.35 (dd, J = 16.2, 6.7 Hz, 1 H, CH₂COOH), 2.15-2.10 (m, 1 H,

CH=CHCH₂), 2.00 (s, 3 H, CH=C(CH₃)), 1.99-1.95 (m, 1 H, CH=CHCH₂), 1.48-1.30 (m, 5 H, CH(CH₃), 2 x CH₂), 1.18 (s, 3 H, C(CH₃)₂), 1.08 (s, 3 H, C(CH₃)₂), 1.05 (d, J = 6.7 Hz, 3 H, CH(CH₃)), 0.89-0.84 (m, 21 H, CH(CH₃)),
 5 SiC(CH₃)₃), 0.09 (s, 3 H, Si(CH₃)₂), 0.05 (s, 3 H, Si(CH₃)₂), 0.04 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 218.9, 175.4, 166.3, 152.8, 143.5, 134.4, 125.7, 119.5, 115.9, 74.4, 54.7, 45.5, 40.9, 40.0, 34.3, 31.9, 30.6, 28.9, 28.8,
 10 27.0, 26.8, 26.7, 24.4, 20.0, 19.6, 19.3, 19.1, 17.9, 17.1, 15.5, -2.9, -3.1, -3.3, -3.8; FAB HRMS (NBA/CsI) m/e 856.3459, M + Cs⁺ calcd for C₃₈H₆₉NO₆SSi₂ 856.3439.

Synthesis of Hydroxy Acid 107 as illustrated in
 15 Figure 14. Selective Desilylation of tris(Silyl) Ether 106. Carboxylic acid 106 (150 mg, 0.18 mmol) was converted to hydroxy acid 107 (107 mg, 82%) according to the procedure described above for 72. 107: Yellow oil; R_f = 0.45 (silica gel, 5% MeOH in Methylene chloride); [α]_D²² -8.0 (c 0.2, CHCl₃); IR (thin film) ν_{max} 3225, 2943, 2860, 1719, 1690, 1461, 1384, 1296, 1250, 1190, 1085, 985, 832,
 20 761, 667 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.93 (s, 1 H SCH=C), 6.60 (s, 1 H, CH=CCH₃), 5.54-5.50 (m, 1 H, CH=CH), 5.40-5.34 (m, 1 H, CH=CH), 4.54 (dd, J = 6.4, 3.7 Hz, 1 H, (CH₃)₂CCHOSi), 4.15 (dd, J = 6.5, 6.3 Hz, 1 H, CH₂CHOH), 3.82 (d, J = 7.6 Hz, 1 H, CH(CH₃)CHOSi), 3.09 (dq, J = 6.9, 6.5 Hz, 1 H, C(O)CHCH₃), 2.71 (s, 3 H, N=C(CH₃)S), 2.37-2.32 (m, 3 H, CH₂CH=CH, CH₂COOH), 2.30 (dd, J = 16.3, 6.4 Hz, 1 H, CH₂COOH), 2.15-2.10 (m, 2 H,

CH=CHCH₂), 1.97 (s, 3 H, CH=C(CH₃)), 1.36-1.18 (m, 5 H, CH(CH₃), 2 x CH₂), 1.17 (s, 3 H, C(CH₃)₂), 1.07 (s, 3 H, C(CH₃)₂), 1.05 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 0.88 (s, 9 H, SiC(CH₃)₃), 0.85-0.82 (m, 12 H, CH(CH₃), SiC(CH₃)₃), 0.07 (s, 3 H, Si(CH₃)₂), 0.06 (s, 3 H, Si(CH₃)₂), 0.05 (s, 6 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 218.2, 175.4, 165.4, 152.2, 142.0, 133.1, 124.9, 118.6, 115.1, 74.4, 53.8, 45.8, 40.2, 38.9, 37.7, 34.8, 33.2, 27.9, 27.5, 27.1, 26.2, 26.1, 26.0, 22.6, 21.4, 18.8, 18.6, 16.9, 14.5, 13.3, -3.4, -3.6, -4.3, -4.6; FAB HRMS (NBA/CsI) m/e 856.3402, M + Cs⁺ calcd for C₃₈H₆₉NO₆SSi₂ 856.3439.

Synthesis of Lactone 108 as illustrated in Figure 14. Macrolactonization of Hydroxy Acid 72. A solution of hydroxy acid 72 (200 mg, 0.28 mmol) in THF (4 mL) was treated at 0 °C with Et₃N (0.23 mL, 1.68 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (0.22 mL, 1.40 mmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 15 min, and then added to a solution of 4-DMAP (342 mg, 2.80 mmol, 10.0 equiv) in toluene (140 mL) at 25 °C and stirred at that temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40% ether in hexanes, and the resulting solution was concentrated. Purification by flash column chromatography (silica gel, 2% MeOH in Methylene chloride) furnished lactone 108 (178 mg, 90%) as a colorless oil: R_f = 0.37 (silica gel, 30% ether in hexanes); [α]_D²² -22.9

(c 0.3, CHCl₃); IR (thin film) ν_{max} 2925, 2854, 1734, 1693, 1464, 1381, 1252, 1187, 1158, 1099, 988, 829, 758 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.98 (s, 1 H, SCH=C), 6.58 (s, 1 H, CH=CCH₃), 5.53 (m, 1 H, CH=CH), 5.43-5.34 (m, 1 H, CH=CH), 5.00 (d, J = 10.2 Hz, 1 H, O=COCH), 4.03 (d, J = 10.5 Hz, 1 H, CHOSi), 3.89 (d, J = 9.0 Hz, 1 H, CHOSi), 2.98 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)CHCH₃), 2.85 (d, J = 16.7 Hz, 1 H, CH₂COO), 2.72 (s, 3 H, N=C(CH₃)S), 2.66 (dd, J = 16.7, 10.7 Hz, 1 H, CH₂COO), 2.40-2.30 (m, 1 H, CH=CHCH₂), 2.11 (s, 3 H, CH=C(CH₃)), 2.10-2.04 (m, 2 H, CH₂CH=CH), 1.92-1.83 (m, 1 H, CH=CHCH₂), 1.66-1.38 (m, 5 H, CH(CH₃), 2 x CH₂), 1.17 (s, 3 H, C(CH₃)₂), 1.13 (s, 3 H, C(CH₃)₂), 1.06 (d, J = 7.0 Hz, 3 H, CH(CH₃)), 0.94 (d, J = 7.0 Hz, 3 H, CH(CH₃)), 0.92 (s, 9 H, SiC(CH₃)₃), 0.83 (s, 9 H, SiC(CH₃)₃), 0.09 (s, 3 H, Si(CH₃)₂), 0.07 (s, 3 H, Si(CH₃)₂), 0.05 (s, 3 H, Si(CH₃)₂), -0.12 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 215.0, 171.3, 165.4, 135.7, 135.1, 125.8, 122.7, 119.9, 115.9, 79.5, 76.4, 53.3, 48.0, 38.8, 31.7, 31.3, 29.7, 29.2, 28.4, 26.4, 26.2, 26.1, 25.9, 24.2, 19.1, 18.7, 18.6, 17.7, 15.3, -3.1, -3.2, -3.7, -5.8; FAB HRMS (NBA) m/e 706.4382, M + H⁺ calcd for C₃₈H₆₇NO₅SSi₂ 706.4357.

Synthesis of Lactone 109 as illustrated in Figure 14. Macrolactonization of Hydroxy Acid 107. The cyclization of hydroxy acid 107 (100 mg, 0.14 mmol) was carried out exactly as described for 108 above and yielded lactone 109 (84 mg, 85%) as a colorless oil: R_f = 0.40 (silica gel, 30% ether in hexanes); [α]_D²⁵ -40.5 (c 0.2,

CHCl₃); IR (thin film) ν_{max} 2929, 2855, 1739, 1690, 1469, 1384, 1253, 1180, 1089, 1053, 985, 835, 775 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.94 (s, 1 H, SCH=C), 6.53 (s, 1 H, CH=CCH₃), 5.55-5.46 (m, 1 H, CH=CH), 5.39-5.30 (m, 1 H, CH=CH), 5.32 (dd, J = 7.0, 3.0 Hz, 1 H, O=COCH), 4.43 (dd, J = 7.5, 2.9 Hz, 1 H, CHOSi), 3.99 (d, J = 7.1 Hz, 1 H, CHOSi), 3.20 (dq, J = 7.3, 7.1 Hz, 1 H, C(O)CHCH₃), 2.71 (s, 3 H, N=C(CH₃)S), 2.59 (m, 1 H, CH=CHCH₂), 2.21 (dd, J = 14.6, 3.2 Hz, 1 H, CH₂COO), 2.20 (dd, J = 14.6, 7.6 Hz, 1 H, CH₂COO), 2.16 (s, 3 H, CH=C(CH₃)), 2.15-1.95 (m, 3 H, CH=CHCH₂, CH₂CH=CH), 1.60-1.50 (m, 3 H, CH(CH₃), 2 x CH₂), 1.47-1.35 (m, 2 H, CH(CH₃), 2 x CH₂), 1.24 (s, 3 H, C(CH₃)₂), 1.11 (d, J = 7.2 Hz, 3 H, CH(CH₃)), 1.09 (s, 3 H, C(CH₃)₂), 0.90 (s, 9 H, SiC(CH₃)₃), 0.86 (s, 9 H, SiC(CH₃)₃), 0.83 (d, J = 6.7 Hz, 3 H, CH(CH₃)), 0.09 (s, 6 H, 2 x Si(CH₃)₂), 0.01 (s, 3 H, Si(CH₃)₂), -0.05 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 221.2, 171.6, 165.8, 134.9, 134.1, 125.7, 125.2, 120.7, 117.1, 78.8, 75.2, 74.5, 54.3, 48.1, 42.5, 37.9, 33.7, 32.4, 26.8, 26.7, 26.5, 26.2, 25.8, 19.7, 19.2, 19.0, 18.8, 17.7, 15.9, 14.1, -3.0, -3.3, -3.7, -4.3; FAB HRMS (NBA) m/e 706.4333, M + H⁺ calcd for C₃₈H₆₇NO₅SSi₂ 706.4357.

Synthesis of Dihydroxy Lactone 70 as illustrated in Figure 14. To lactone 108 (50 mg, 0.071 mmol), cooled to -20 °C, was added a freshly prepared 20% (v/v) CF₃COOH solution in Methylene chloride (400 mL). The reaction mixture was allowed to reach 0 °C and was stirred for 1 h at that temperature. The solvents were evaporated

under reduced pressure and the crude product was purified by preparative thin layer chromatography (silica gel, 6% MeOH in Methylene chloride) to afford pure dihydroxy lactone 70 (31 mg, 92%): $R_f = 0.38$ (silica gel, 5% MeOH in Methylene chloride); $[\alpha]_{22D} -80.2$ (c 1.7, $CHCl_3$); IR (thin film) ν_{max} 3470, 2929, 1733, 1686, 1464, 1380, 1250, 1182, 1045, 978, 732 cm^{-1} ; 1H NMR (500 MHz, C_6D_6) δ 6.83 (s, 1 H, SCH=C), 6.56 (s, 1 H, CH=CCH₃), 5.48 (dd, $J = 7.0, 3.0$ Hz, 1 H, O=COCH), 5.43-5.41 (m, 2 H, CH=CH), 4.21 (d, $J = 11.5$ Hz, 1 H, CHOH), 3.77 (bs, 1 H, CHOH), 3.13 (bs, 1 H, OH), 3.01 (bs, 1 H, OH), 2.95 (m, 1 H, C(O)CHCH₃), 2.70-2.62 (m, 1 H, CH₂COO), 2.47 (ddd, $J = 14.6, 11.5$ Hz, 1 H, CH₂COO), 2.27 (s, 3 H, N=C(CH₃)S), 2.18-2.12 (m, 2 H, CH=CHCH₂), 2.15 (s, 3 H, CH=C(CH₃)), 1.97-1.83 (m, 2H, CH₂CH=CH), 1.56-1.50 (m, 1 H, CH(CH₃)), 1.41-1.22 (m, 4 H, 2 x CH₂), 1.15 (d, $J = 7.0$ Hz, 3 H, CH(CH₃)), 1.07 (d, $J = 6.0$ Hz, 3 H, CH(CH₃)), 1.07 (s, 3 H, C(CH₃)₂), 1.06 (s, 3 H, C(CH₃)₂); ^{13}C NMR (150.9 MHz, C_6D_6) δ 220.2, 170.6, 165.4, 153.8, 139.2, 134.1, 126.1, 120.4, 116.9, 79.2, 74.9, 73.2, 54.2, 42.5, 40.3, 39.5, 32.9, 32.6, 28.6, 28.4, 23.3, 19.3, 19.1, 16.4, 16.3, 14.4; FAB HRMS (NBA/CsI) m/e 610.1580, $M + Cs^+$ calcd for $C_{26}H_{39}NO_5S$ 610.1603.

Synthesis of Dihydroxy Lactone 110 as illustrated in Figure 14. Lactone 109 (38.0 mg, 0.054 mmol) was treated with CF_3COOH in exactly the same way as described above for 70, yielding dihydroxy lactone 110 (24.5 mg, 95%): $R_f = 0.30$ (silica gel, 6% MeOH in Methylene

chloride); $[\alpha]_{22D} -93.1$ (c 0.1, CHCl_3); IR (thin film) ν_{max} 3450, 2929, 1735, 1685, 1464, 1380, 1250, 1182, 1045, 978, 732 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.96 (s, 1 H, $\text{SCH}=\text{C}$), 6.51 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.60-5.50 (m, 2 H, $\text{CH}=\text{CH}$), 5.40-5.32 (m, 1 H, $\text{O}=\text{COCH}$), 4.25 (d, $J = 9.5$ Hz, 1 H, CHOH), 3.55 (d, $J = 9.6$ Hz, 1 H, CHOH), 3.39 (bs, 1 H, OH), 3.31 (dq, $J = 6.9, 6.7$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.99 (bs, 1 H, OH), 2.71 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.69-2.61 (m, 1 H, $\text{CH}=\text{CHCH}_2$), 2.59 (d, $J = 16.3$ Hz, 1 H, CH_2COO), 2.45-2.35 (m, 2 H, CH_2COO , $\text{CH}=\text{CHCH}_2$), 2.20-2.10 (m, 1 H, $\text{CH}_2\text{CH}=\text{CH}$), 2.08 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.98-1.90 (m, 1 H, $\text{CH}_2\text{CH}=\text{CH}$), 1.59-1.50 (m, 1 H, $\text{CH}(\text{CH}_3)$), 1.49-1.30 (m, 4 H, 2 x CH_2), 1.17 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.11 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.03 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.01 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 222.2, 171.1, 165.2, 153.5, 139.5, 133.2, 125.1, 120.0, 116.7, 78.4, 74.1, 72.9, 52.5, 40.7, 39.5, 37.9, 34.5, 32.7, 31.3, 27.6, 24.7, 22.2, 18.9, 17.5, 15.5, 15.3; FAB HRMS (NBA) m/e 478.2610, $M + H^+$ calcd for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$ 478.2627.

Synthesis of Epothilone A (1) as illustrated in Figure 14. Epoxidation of Lactone 70 with Methyl(trifluoromethyl)dioxirane. To a solution of 70 (10 mg, 21.0 μmol) in MeCN (200 mL) was added 4.10 - 4.00 M aqueous solution of disodium ethylenediaminetetraacetate (Na_2EDTA , 120 mL; Aldrich) and the reaction mixture was cooled to 0 $^\circ\text{C}$. 1,1,1-Trifluoroacetone (200 mL) was added followed by a mixture of Oxone $^\circ$ (61 mg, 0.10 μmol , 5.0 equiv) and NaHCO_3 (14.0 mg, 0.17 μmol , 8.0 equiv) with stirring until completion of the reaction was revealed by

TLC. The reaction mixture was treated with excess Me₂S (100 mL) and water (500 mL) and was then extracted with EtOAc (4 x 2 mL). The combined organic phase was dried (MgSO₄), filtered, and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) gave a mixture of epothilones A (1) and its α -epoxide epimer (8.6 mg, 78% total yield). A second preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) furnished pure epothilone A (1) (6.4 mg, 65%) as a white solid.. 1: R_f = 0.23 (silica gel, 5% MeOH in Methylene chloride); [a]_D²² -45.0 (c 0.02, MeOH); IR (thin film) ν_{max} 3476, 2974, 1738, 1692 cm⁻¹; ¹H NMR (600 MHz, C₆D₆) δ 6.71 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.45 (dd, J = 8.2, 2.3 Hz, 1 H, O=COCH), 4.15 (dd, J = 10.8, 2.9 Hz, 1 H, CHOH), 3.81-3.78 (m, 1 H, CHOH), 3.65 (bs, 1 H, OH), 3.03 (dq, J = 6.9, 6.5 Hz, 1 H, C(O)CHCH₃), 2.77 (ddd, J = 7.9, 4.0, 4.0 Hz, 1 H, CH₂CHO), 2.62-2.58 (m, 1 H, CH₂CHO), 2.40 (dd, J = 14.4, 10.8 Hz, 1 H, CH₂COO), 2.26 (bs, 1 H, OH), 2.21 (s, 3 H, N=C(CH₃)S), 2.19 (dd, J = 14.4, 2.9 Hz, 1 H, CH₂COO), 2.05 (s, 3 H, CH=C(CH₃)), 1.86 (ddd, J = 15.2, 2.5, 2.5 Hz, 1 H, CH₂CHO), 1.81-1.74 (m, 1 H, CH₂CHO), 1.68 (ddd, J = 15.2, 7.6, 7.6 Hz, 1 H, CH₂CHO), 1.53-1.49 (m, 1 H, CH₂CHO), 1.40-1.15 (m, 5 H, CH(CH₃), 2 x CH₂), 1.06 (d, J = 7.0 Hz, 3 H, CH(CH₃)), 1.03 (s, 3 H, C(CH₃)₂), 0.97 (s, 3 H, C(CH₃)₂), 0.95 (d, J = 6.9 Hz, 3 H, CH(CH₃)); ¹³C NMR (150.9 MHz, C₆D₆) δ 219.0, 170.2, 164.7, 153.0, 137.5, 119.9, 116.6, 76.6, 75.2, 73.5, 57.2, 54.2, 52.9, 43.8, 39.1, 36.3, 31.7, 30.3, 27.3, 23.9, 21.1, 20.6,

18.7, 17.4, 15.7, 14.6; HRMS (FAB), calcd for C₂₆H₃₉CsNO₆S (M + Cs⁺) 626.1552, found 626.1531.

Synthesis of 6S,7R-Epothilones 111 and 112 as illustrated in Figure 14. Epoxidation of Lactone 110. To a solution of lactone 110 (9.0 mg, 18.8 mmol) in MeCN (0.5 mL) was added disodium ethylenediaminetetraacetate (Na₂EDTA, 4.10⁻⁴ M aqueous solution, 200 mL) and 1,1,1-trifluoroacetone (200 mL) at 0 °C. The resulting solution was stirred at 0 °C while a mixture of solid Oxone® (58 mg, 94.0 mmol, 5.0 equiv) and NaHCO₃ (14.0 mg, 0.17 mmol, 8.8 equiv) was added portionwise until completion of the reaction was established by TLC). The reaction mixture was treated with excess Me₂S (100 mL) and water (500 mL) and was extracted with EtOAc (4 x 2 mL). The combined organic phase was dried (MgSO₄), filtered, and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) gave a mixture of epothilones 111 and 112 (8.1 mg, 87% total yield, ca 2:1 ratio by ¹H NMR). The major diastereoisomer (111, stereochemistry unassigned) was isolated by preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) (5.4 mg, 58%) and exhibited the following properties: R_f = 0.23 (silica gel, 6% MeOH in Methylene chloride); [α]_D²⁵ -20.0 (c 0.2, CHCl₃); IR (thin film) ν_{max} 3448, 2919, 1725, 1684, 1455, 1378, 1284, 1149, 1061, 1020, 973, 750 cm⁻¹; ¹H NMR (500 MHz, CHCl₃) δ 6.99 (s, 1 H, SCH=C), 6.68 (s, 1 H, CH=CCH₃), 5.64-5.61 (m, 1 H, O=COCH), 4.43 (d, J = 2.1 Hz, 1 H, OH), 4.29

(ddd, $J = 7.6, 2.5, 2.5$ Hz, 1 H, CHOH), 3.82 (d, $J = 8.2$ Hz, 1 H, CHOH), 3.35 (bs, 1 H, OH), 3.22 (q, $J = 7.0$ Hz, 1 H, C(O)CHCH₃), 3.14 (ddd, $J = 10.3, 4.1, 3.2$ Hz, 1 H, CH₂CHO), 2.90 (ddd, $J = 10.3, 4.3, 2.3$ Hz, 1 H, CH₂CHO),
 5 2.71 (s, 3 H, N=C(CH₃)S), 2.54 (dd, $J = 13.7, 7.6$ Hz, 1 H, CH₂COO), 2.51 (dd, $J = 13.7, 2.5$ Hz, 1 H, CH₂COO),
 2.21-2.19 (m, 1 H, CH₂CHO), 2.18 (s, 3 H, CH=C(CH₃)),
 1.94 (ddd, $J = 15.3, 10.3, 3.7$ Hz, 1 H, CH₂CHO), 1.77-
 1.69 (m, 2 H, CH₂CHO), 1.60-1.00 (m, 5 H, CH(CH₃), 2 x
 10 CH₂), 1.15 (s, 3 H, C(CH₃)₂), 1.14 (d, $J = 6.9$ Hz, 3 H, CH(CH₃)), 1.06 (s, 3 H, C(CH₃)₂), 1.02 (d, $J = 7.0$ Hz, 3 H, CH(CH₃)); ¹³C NMR (150.9 MHz, CHCl₃) δ 221.8, 172.1, 165.1, 152.6, 134.7, 119.8, 116.8, 76.0, 74.4, 72.8, 56.4, 53.8, 53.0, 40.2, 39.1, 34.1, 32.7, 29.4, 27.8, 22.7,
 15 20.9, 19.0, 16.1, 15.9, 15.0, 11.8; FAB HRMS (NBA) m/e 494.2587, M + H⁺ calcd for C₂₆H₃₉NO₆S 494.2576.

Synthesis of Olefinic Compound 115 as illustrated
 in Figure 16. Phosphonium salt 79 (9.0 g, 12.93 mmol,
 20 1.5 equiv; *vide supra*) was dissolved in THF (90 mL) and
 the solution was cooled to 0 °C. Sodium
 bis(trimethylsilyl)amide (NaHMDS, 1.0 M solution in THF,
 12.84 mL, 12.84 mmol, 1.48 equiv) was slowly added and the
 resulting mixture was stirred at 0 °C for 15 min. The
 25 reaction mixture was then cooled to -20 °C before ketone
 78 (2.23 g, 8.62 mmol, 1.0 equiv) in THF (10 mL) was added
 and the reaction mixture was stirred at the same
 temperature for 12 h. Saturated aqueous NH₄Cl solution
 (50 mL) was added and the mixture was extracted with ether

(200 mL). The organic phase was washed with brine (2 x 100 mL), dried (MgSO₄) and concentrated to afford, after flash column chromatography (silica gel, 2% ether in hexanes) olefins 115 (3.8g, 73%, Z:E ca. 1:1 by ¹H NMR):

5 R_f = 0.56 (silica gel, 20% ether in hexanes); IR (thin film) ν_{max} 2931, 2857, 1465, 1386, 1253, 1089, 942, 838, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.90, 6.89 (singlets, 1 H total, SCH=C), 6.44 (s, 1 H, CH=CCH₃), 5.15-5.10 (m, 1 H, C(CH₃)=CH), 4.08 (m, 1 H, CHOSi), 3.42 (m, 1 H, CH₂OSi), 3.33 (dd, J = 13.3, 6.8 Hz, 0.5 H, CH₂OSi), 3.32 (dd, J = 13.3, 6.7 Hz, 0.5 H, CH₂OSi), 2.69 (s, 3 H, N=C(S)CH₃), 2.31-2.19 (m, 2 H, CH₂CHOSi), 1.99 (s, 3 H, CH=CCH₃), 1.99-1.96 (m, 1 H, CH₂C(CH₃)=CH), 1.95-1.91 (m, 1 H, CH₂C(CH₃)=CH), 1.65 (s, 1.5 H, C(CH₃)=CH), 1.58 (s, 1.5 H, C(CH₃)=CH), 1.56-1.52 (m, 1 H), 1.43-1.28 (m, 3 H), 1.05-0.97 (m, 1 H), 0.88 (s, 18 H, 2 x Si(CH₃)₃), 0.86 (d, J = 6.8 Hz, 1.5 H, CH₃CH), 0.83 (d, J = 6.7 Hz, 1.5 H, CH₃CH), 0.04 (s, 3 H, Si(CH₃)₂), 0.02 (s, 3 H, Si(CH₃)₂), 0.01 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.2, 153.3, 142.7, 142.6, 136.9, 136.8, 121.4, 120.6, 118.6, 118.5, 114.9, 114.8, 79.0, 78.8, 68.3, 40.1, 35.8, 35.7, 35.5, 35.4, 33.2, 32.9, 32.3, 25.9, 25.8, 25.4, 25.3, 23.5, 19.2, 18.3, 18.2, 16.7, 16.2, 13.9, -4.6, -4.9, -5.3; FAB HRMS (NBA) m/e

10 252.3710, M + H⁺ calcd for C₃₀H₅₇NO₂SSi₂ 552.3727.

Synthesis of Hydroxy Olefins 116 as illustrated in Figure 16. Desilylation of Silylether 115. Silylether 115 (3.80 g, 6.88 mmol) was dissolved in Methylene

chloride : MeOH (1:1, 70 mL) and the solution was cooled to 0 °C prior to addition of CSA (1.68 g, 7.23 mmol, 1.05 equiv) during a 5 min period. The resulting mixture was stirred for 30 min at 0 °C, and then for 1 h at 25 °C.

5 Et3N (1.57 mL, 7.23 mmol, 1.05 equiv) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished pure hydroxy compound 116 (2.9 g, 97%): Rf = 0.33 (silica gel, 50% ether in hexanes); IR (thin

10 film) ν_{max} 3370, 2929, 2857, 1463, 1382, 1252, 1185, 1072, 836, 776 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) (mixture of Z:E olefins, ca 1:1) δ 6.91, 6.90 (singlets, 1 H total, $\text{SCH}=\text{C}$), 6.43, 6.41 (singlets, 1 H total, $\text{CH}=\text{CCH}_3$), 5.14 (t, J = 6.9 Hz, 0.5 H, $\text{C}(\text{CH}_3)=\text{CH}$), 5.06 (t, J = 6.8 Hz, 0.5 H, $\text{C}(\text{CH}_3)=\text{CH}$), 4.08 (m, 1 H, CHOSi), 3.47 (dd, J = 10.4, 5.9 Hz, 0.5 H, CH_2OH), 3.41 (dd, J = 10.6, 6.1 Hz, 0.5 H, CH_2OH), 3.40-3.36 (m, 1 H, CH_2OH), 2.68 (s, 3 H, $\text{N}=\text{C}(\text{S})\text{CH}_3$), 2.31-2.18 (m, 2 H, CH_2CHOSi), 2.05-1.99 (m, 1 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.96, 1.95 (singlets, 3 H total, $\text{CH}=\text{CCH}_3$), 1.95-1.93 (m, 1 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.65 (s, 1.5 H, $\text{C}(\text{CH}_3)=\text{CH}$), 1.56 (s, 1.5 H, $\text{C}(\text{CH}_3)=\text{CH}$), 1.60-1.51 (m, 1 H), 1.52-1.27 (m, 3 H), 1.10-0.96 (m, 1 H), 0.89 (d, J = 6.9 Hz, 1.5 H, CH_3CH), 0.87 (s, 9 H, $\text{SiC}(\text{CH}_3)_3$), 0.85 (d, J = 6.8 Hz, 1.5 H, CH_3CH), 0.04, 0.03 (singlets, 3 H total, $\text{Si}(\text{CH}_3)_2$), -0.01, -0.02 (singlets, 3 H total, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 164.5, 164.4, 153.0, 152.9, 142.7, 142.3, 136.7, 136.5, 121.5, 120.5, 118.8, 118.6, 114.9, 114.8, 114.7, 79.1, 78.8, 68.2, 68.1, 39.7, 35.7, 35.6, 35.4, 35.2, 33.0, 32.4, 32.1,

25

25.9, 25.2, 24.8, 23.4, 19.1, 18.9, 18.2, 18.1, 16.6,
16.3, 15.9, 13.9, 13.7, -4.7, -4.9; FAB HRMS (NBA) m/e
438.2875, M + H⁺ calcd for C₂₄H₄₃NO₂SSi 438.28.

5 **Synthesis of Aldehyde 75' as illustrated in Figure**
16. Oxidation of Alcohol 116. Alcohol 116 (mixtures of
Z and E geometrical isomers, 4.60 g, 10.64 mmol) was
dissolved in Methylene chloride (105 mL, 0.1 M). DMSO (35
mL), Et₃N (7.4 mL, 53.20 mmol, 5.0 equiv) and SO₃·pyr (3.4
10 g, 21.28 mmol, 2.0 equiv) were added at 25 °C and the
resulting mixture was stirred for 30 min. Saturated
aqueous NH₄Cl solution (50 mL) and ether (300 mL) were
added, and the organic phase was separated and washed with
brine (2 x 30 mL), dried (MgSO₄), and concentrated under
15 reduced pressure. Flash column chromatography (silica
gel, 20% ether in hexanes) furnished aldehyde 75' (4.40 g,
mixture of Z:E isomers, ca 1:1, 95%): R_f = 0.48 (silica
gel, 50% ether in hexanes); IR (thin film) ν_{max} 2931,
2860, 1725, 1495, 1455, 1378, 1249, 1173, 1073, 938, 832,
20 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.60, (d, J = 1.9 Hz,
0.5 H, CHO), 9.55 (d, J = 1.9 Hz, 0.5 H, CHO), 6.92, 6.91
(singlets, 1 H total, SCH=C), 6.45, 6.44 (singlets, 1 H
total, CH=CCH₃), 5.18-5.13 (m, 1 H, CH₂CH=CCH₃), 4.12-4.07
(m, 1 H, CHOSi), 2.71, 2.70 (singlets, 3 H total,
25 N=C(S)CH₃), 2.36-2.20 (m, 3 H), 2.07-1.90 (m, 1 H), 1.99
(s, 3 H, CH=CCH₃), 1.71-1.60 (m, 1 H), 1.66 (d, J = 1.0
Hz, 1.5 H, CH₂CH=CCH₃), 1.58 (d, J = 1.0 Hz, 1.5 H,
CH₂CH=CCH₃), 1.43-1.25 (m, 4 H), 1.08 (d, J = 7.0 Hz, 1.5
H, CH₃CH), 1.04 (d, J = 7.0 Hz, 1.5 H, CH₃CH), 0.88 (s, 9

H, SiC(CH₃)₃), 0.05, 0.04 (singlets, 3 H total, Si(CH₃)₂),
 -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ
 205.2, 205.0, 164.4, 153.1, 142.3, 136.0, 135.9, 122.0,
 121.2, 118.7, 118.6, 115.0, 114.9, 78.8, 78.7, 46.2, 46.1,
 35.4, 35.3, 31.7, 31.6, 30.2, 30.0, 25.7, 25.1, 25.0,
 23.3, 22.6, 19.1, 18.2, 16.1, 14.0, 13.9, 13.8, 13.3,
 13.2, -4.8, -5.1; FAB HRMS (NBA) m/e 436.2715, M + H⁺
 calcd for C₂₄H₄₁NO₂SSi 436.2706.

Synthesis of tris(Silylethers) 119' and 120' as

illustrated in Figure 16. Aldol Reaction of Keto Acid
 76 with Aldehyde 75'. A solution of keto acid 76 (773 mg,
 2.56 mmol, 1.2 equiv; *vide supra*) in THF (7.0 mL) was
 reacted with aldehyde 75' (930 mg, mixture of Z:E olefins,
 ca 1:1, 2.13 mmol, 1.0 equiv) according to the same
 procedure as described above for the condensation of 76
 and 74 (Figure 14), to afford, after similar processing,
 pure carboxylic acids 119' (564 mg, mixture of Z and E
 isomers, ca 1:1, 31% from 8') and 120' (545 mg, mixture of
 Z and E isomers, ca 1:1, 30% from 8') as colorless oils
 and recovered keto acid 76 (125 mg). 119': R_f = 0.56
 (silica gel, 5% MeOH in Methylene chloride); IR (thin
 film) ν_{max} 2942, 2856, 1706, 1464, 1388, 1361, 1248, 1183,
 1087, 989, 833, 774, 731 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ
 6.89 (s, 1 H, SCH=C), 6.50, 6.49 (singlets, 1 H total,
 CH=CCH₃), 5.15 (m, 1 H, (CH₃)C=CHCH₂), 4.39 (m, 1 H,
 (CH₃)₂CCHOSi), 4.10-4.03 (m, 1 H, CH₂CHOSi), 3.78-3.70 (m,
 1 H, CH(CH₃)CHOSi), 3.13 (dq, J = 7.2, 6.7 Hz, 1 H,
 C(O)CH(CH₃)), 2.68 (s, 3 H, N=C(CH₃)S), 2.49 (dd, J =

16.4, 2.6 Hz, 0.5 H, CH₂COOH), 2.44 (dd, J = 16.4, 3.1 Hz, 0.5 H, CH₂COOH), 2.31-2.15 (m, 3 H, CH₂COOH, CH₂C(CH₃)=CHCH₂), 2.05-1.85 (m, 2 H, CH₂C(CH₃)=CH), 1.95 (s, 1.5 H, CH=C(CH₃)), 1.94 (s, 1.5 H, CH=C(CH₃)), 1.64 (s, 1.5 H, CH₂C(CH₃)=CH), 1.55 (s, 1.5 H, CH₂C(CH₃)=CH), 1.45-1.25 (m, 4 H), 1.19 (s, 3 H, C(CH₃)₂), 1.10 (s, 3 H, C(CH₃)₂), 1.21-1.09 (m, 1 H), 1.06 (d, J = 6.8 Hz, 1.5 H, CH(CH₃)), 1.05 (d, J = 6.8 Hz, 1.5 H, CH(CH₃)), 0.90-0.85 (m, 30 H, CH(CH₃), 3 x SiC(CH₃)₃), 0.10 (s, 1.5 H, Si(CH₃)₂), 0.08 (s, 1.5 H, Si(CH₃)₂), 0.07 (s, 1.5 H, Si(CH₃)₂), 0.05 (s, 1.5 H, Si(CH₃)₂), 0.04 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂), 0.02 (s, 3 H, Si(CH₃)₂), -0.02 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 218.1, 217.9, 176.7, 176.6, 164.8, 152.8, 142.9, 142.8, 136.7, 121.5, 120.5, 118.4, 118.3, 114.6, 78.9, 78.8, 77.7, 77.3, 73.5, 73.4, 53.5, 53.4, 45.3, 44.8, 40.4, 40.1, 38.9, 38.6, 35.4, 35.3, 32.5, 31.0, 30.4, 26.2, 26.0, 25.8, 25.7, 25.6, 23.5, 23.4, 19.1, 18.8, 18.7, 18.5, 18.4, 18.2, 17.8, 17.6, 17.3, 16.2, 15.8, 15.6, 13.9, 13.8, -3.6, -3.7, -3.9, -4.2, -4.3, -4.6, -4.7, -5.0; FAB HRMS (NBA/CsI) m/e 984.4422, M + Cs+ calcd for C₄₅H₈₅NO₆SSi₃ 984.4460. 53': R_f = 0.65 (silica gel, 5% MeOH in Methylene chloride); IR (thin film) ν_{max} 2954, 2856, 1713, 1470, 1386, 1253, 1080, 988, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.13 (dd, J = 7.0, 6.9 Hz, 0.5 H, (CH₃)C=CHCH₂), 5.09 (dd, J = 7.1, 6.9 Hz, 0.5 H, (CH₃)C=CHCH₂), 4.58 (dd, J = 6.1, 3.5 Hz, 0.5 H, (CF₃)₂CCCHOSi), 4.56 (dd, J = 6.0, 3.5 Hz, 0.5 H,

(CH₃)₂CCHOSi), 4.16 (dd, J = 6.7, 6.6 Hz, 0.5 H, CH₂CHOSi), 4.06 (dd, J = 6.7, 6.0 Hz, 0.5 H, CH₂CHOSi), 3.85-3.80 (m, 1 H, CH(CH₃)CHOSi), 3.11 (dq, J = 7.1, 7.0 Hz, 1 H, C(O)CH(CH₃)), 2.74 (s, 3 H, N=C(CH₃)S), 2.43-2.10 (m, 4 H), 1.96-1.80 (m, 2 H), 1.92 (s, 1.5 H, CH=C(CH₃)), 1.91 (s, 1.5 H, CH=C(CH₃)), 1.66 (s, 1.5 H, CH₂C(CH₃)=CH), 1.56 (s, 1.5 H, CH₂C(CH₃)=CH), 1.35-1.02 (m, 14 H, CH(CH₃), 2 x CH₂, C(CH₃)₂, C(CH₃)₂, CH(CH₃)), 0.92-0.80 (m, 30 H, 3 x SiC(CH₃)₃, CH(CH₃)), 0.10--0.03 (m, 18 H, 3 x Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 218.1, 217.9, 174.8, 174.7, 165.6, 165.5, 152.4, 143.6, 137.0, 136.8, 121.4, 121.0, 118.4, 117.9, 114.4, 78.9, 78.6, 76.4, 72.4, 72.3, 53.9, 53.8, 45.8, 45.7, 40.3, 40.2, 39.4, 38.4, 37.5, 35.6, 35.3, 35.0, 34.7, 32.2, 26.6, 26.3, 26.0, 25.8, 25.6, 23.8, 23.1, 22.7, 19.1, 18.7, 18.6, 18.5, 18.4, 18.2, 17.1, 16.9, 14.0, 13.8, 13.6, 13.4, -3.4, -3.6, -4.3, -4.6, -4.7, -4.9; FAB HRMS (NBA/CsI) m/e 984.4489, M + Cs⁺ calcd for C₄₅H₈₅NO₆SSi₃ 984.4460.

Synthesis of Hydroxy Acid 73' as illustrated in Figure 16. Selective Desilylation of 119'. Carboxylic acid 119' (300 mg, mixture of Z and E isomers, ca 1 : 1, 0.35 mmol) was converted to hydroxy acid 73' (194 mg, mixture of Z and E isomers, ca 1:1, 75%) according to the same procedure described above for hydroxy acid 72 (Figure 14). Compound 73': Yellow oil; R_f = 0.41 (silica gel, 5% MeOH in Methylene chloride); IR (thin film) ν_{max} 3260, 2923, 2852, 1707, 1463, 1381, 1249, 1187, 1085, 984, 831, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.05, 6.94 (singlets,

1 H total, SCH=C), 6.62, 6.57 (singlets, 1 H total,
 CH=CCH₃), 5.20-5.14 (m, 1 H, CH₃C=CHCH₂), 4.41 (dd, J =
 6.0, 3.5 Hz, 0.5 H, (CH₃)₂CCHOSi), 4.37 (dd, J = 7.0, 3.0
 Hz, 0.5 H, (CH₃)₂CCHOSi), 4.16 (dd, J = 6.6, 6.5 Hz, 1
 5 H, CH₂CHOH), 3.77 (d, J = 6.9 Hz, 1 H, CH(CH₃)CHOSi),
 3.17-3.09 (m, 1 H, C(O)CHCH₃), 2.72, 2.71 (singlets, 3 H
 total, N=C(CH₃)S), 2.50 (dd, J = 16.0, 6.0 Hz, 0.5 H,
 CH₂COOH), 2.47 (dd, J = 16.0, 2.7 Hz, 0.5 H, CH₂COOH),
 2.40-2.28 (m, 3 H), 2.17-2.10 (m, 1 H), 2.00 (s, 1.5 H,
 10 CH=C(CH₃)), 1.98 (s, 1.5 H, CH=C(CH₃)), 1.99-1.90 (m, 1
 H), 1.70 (s, 1.5 H, CH₂C(CH₃)=CH), 1.62 (s, 1.5 H,
 CH₂C(CH₃)=CH), 1.53-1.30 (m, 5 H), 1.19 (s, 3 H, C(CH₃)₂),
 1.11 (s, 1.5 H, C(CH₃)₂), 1.10 (s, 1.5 H, C(CH₃)₂), 1.06
 (d, J = 6.7 Hz, 1.5 H, CH(CH₃)), 1.04 (d, J = 6.7 Hz,
 15 1.5 H, CH(CH₃)), 0.89 (s, 18 H, SiC(CH₃)₃), 0.86 (d, J =
 7.0 Hz, 3 H, CH(CH₃)), 0.09 (s, 3 H, Si(CH₃)₂), 0.06 (s, 6
 H, Si(CH₃)₂), 0.05 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz,
 CDCl₃) δ 218.0, 217.9, 176.4, 176.1, 165.0, 164.9, 152.6,
 152.5, 142.1, 141.8, 139.2, 138.9, 120.3, 119.5, 118.8,
 20 118.7, 115.2, 115.1, 77.5, 77.4, 73.4, 73.3, 53.7, 53.5,
 45.1, 44.8, 40.3, 40.1, 38.9, 38.7, 34.1, 34.0, 32.5,
 31.1, 30.5, 26.3, 26.2, 26.0, 23.6, 23.4, 19.2, 19.1,
 18.9, 18.8, 18.5, 18.4, 18.2, 17.6, 17.2, 16.3, 15.9,
 15.8, 14.5, 14.4, -3.6, -3.7, -3.8, -3.9, -4.2, -4.6; FAB
 25 HRMS (NEA/CsI) m/e 870.3564, M + Cs⁺ calcd for
 C₃₉H₇₁NO₆Si₂ 870.3595.

Synthesis of Lactones 121 and 122 as illustrated in
 Figure 16. Macrolactonization of Hydroxy Acid 73'. A

solution of hydroxy acid 73' (140 mg, mixture of Z and E isomers, ca 1:1, 0.189 mmol) in THF (2.6 mL) was treated at 0 °C with Et₃N (58 mL, 0.416 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (29.4 mL, 0.246 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added to a solution of 4-DMAP (233 mg, 1.896 mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 °C and stirred at that temperature for 10 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride), gave pure lactones 121 (50 mg, 37%) and 122 (54 mg, 40%) as colorless oils. 121: R_f = 0.40 (silica gel, 1% MeOH in Methylene chloride); [α]_D²² -11.8 (c 0.8, CHCl₃); IR (thin film) ν_{max} 2931, 2848, 1737, 1690, 1461, 1378, 1249, 1184, 1158, 1097, 1020, 984, 835, 775 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.95 (s, 1 H, SCH=C), 6.56 (s, 1 H, CH=CCH₃), 5.16 (dd, J = 8.4, 7.5 Hz, 1 H, CH₃C=CHCH₂), 4.96 (d, J = 10.1 Hz, 1 H, CH₂COOCH), 4.02 (d, J = 9.9 Hz, 1 H, CHOSi), 3.88 (d, J = 8.9 Hz, 1 H, CHOSi), 3.02 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)CHCH₃), 2.79 (d, J = 15.6 Hz, 1 H, CH₂COOCH), 2.70 (s, 3 H, N=C(CH₃)S), 2.70-2.65 (m, 2 H), 2.48-2.40 (m, 1 H), 2.10 (s, 3 H, CH=C(CH₃)), 2.10-2.04 (m, 2 H), 1.75-1.69 (m, 2 H), 1.67 (s, 3 H, CH₂C(CH₃)=CH), 1.66-1.45 (m, 3 H), 1.18 (s, 3 H, C(CH₃)₂), 1.13 (s, 3 H, C(CH₃)₂), 1.09 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 0.97 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 0.94 (s, 9 H, SiC(CH₃)₃), 0.84 (s, 9 H, SiC(CH₃)₃), 0.10 (s, 3 H,

Si(CH₃)₂, 0.09 (s, 3 H, Si(CH₃)₂), 0.07 (s, 3 H, Si(CH₃)₂), -0.12 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDC13) δ 215.1, 171.2, 164.6, 152.5, 140.6, 138.8, 119.3, 119.1, 115.9, 79.9, 76.3, 53.4, 39.1, 32.4, 31.9, 31.4, 29.7, 27.4, 26.4, 26.1, 26.0, 24.5, 24.3, 23.1, 19.2, 18.7, 18.6, 17.8, 15.3, -3.3, -3.7, -5.7; FAB HRMS (NBA) m/e 720.4534, M + H⁺ calcd for C₃₉H₆₉NO₅SSi₂ 720.4513.

122: R_f = 0.50 (silica gel, 1% MeOH in Methylene chloride); [α]_D²² -22.7 (c 0.6, CHCl₃); IR (thin film) ν_{max} 2931, 2860, 1731, 1696, 1461, 1378, 1249, 1179, 1079, 985, 832, 773 cm⁻¹; ¹H NMR (600 MHz, CDC13) δ 6.92 (s, 1 H, SCH=C), 6.53 (s, 1 H, CH=CCH₃), 5.27 (dd, J = 8.0, 2.7 Hz, 1 H, CH₂COOCH), 5.16 (dd, J = 6.9, 6.6 Hz, 1 H, CH₃C=CHCH₂), 4.47 (t, J = 5.1 Hz, 1 H, CHOSi), 3.89 (dd, J = 4.5, 1.0 Hz, 1 H, CHOSi), 3.05 (dq, J = 6.7, 6.2 Hz, 1 H, C(O)CHCH₃), 2.70 (s, 3 H, N=C(CH₃)S), 2.60 (dd, J = 15.8, 5.8 Hz, 1 H, CH₂COOCH), 2.55 (m, 1 H, CH₃C=CHCH₂), 2.51-2.47 (m, 2 H, CH₂COOCH, CH₃C=CHCH₂), 2.13 (s, 3 H, CH=C(CH₃)), 2.10-2.05 (m, 1 H, CH₂C(CH₃)=CH), 1.91 (m, 1 H, CH₂C(CH₃)=CH), 1.68-1.45 (m, 4 H), 1.57 (s, 3 H, CH₂C(CH₃)=CH), 1.27-1.23 (m, 1 H), 1.17 (s, 3 H, C(CH₃)₂), 1.04 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 1.07 (s, 3 H, C(CH₃)₂), 0.93 (d, J = 6.9 Hz, 3 H, CH(CH₃)), 0.88 (s, 9 H, SiC(CH₃)₃), 0.86 (s, 9 H, SiC(CH₃)₃), 0.07 (s, 6 H, Si(CH₃)₂), 0.06 (s, 3 H, Si(CH₃)₂), 0.05 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDC13) δ 217.2, 171.3, 165.5, 153.6, 139.0, 138.3, 120.9, 120.2, 117.0, 80.1, 77.2, 73.9, 54.8, 44.9, 42.7, 41.1, 40.2, 32.8, 26.9, 26.8, 25.6, 23.5, 21.1, 20.1, 19.2, 19.1, 17.7, 16.8,

16.6, 16.3, -2.7, -3.1, -3.4, -3.6; FAB HRMS (NBA) m/e
720.4533, M + H+ calcd for C₃₉H₆₉NO₅Si₂ 720.4513.

Synthesis of Dihydroxy lactone 71 as illustrated in
Figure 16. Dihydroxy lactone 71 was prepared from
bis(silylether) lactone 121 (13.3 mg, 0.018 mmol) by
treatment with CF₃COOH according to the same procedure
described above for the preparation of 70 (figure 14), to
obtain pure lactone 71 (8.4 mg, 91%) as a colorless oil.
71: R_f = 0.21 (silica gel, 4% MeOH in Methylene chloride);
[α]_D²⁵ -91.5 (c 0.3, CHCl₃); IR (thin film) ν_{max} 3460,
2954, 2919, 1725, 1684, 1455, 1379, 1290, 1249, 1184,
1143, 1043, 1008, 973, 750 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ
6.94 (s, 1 H, SCH=C), 6.57 (s, 1 H, CH=CCH₃), 5.20 (d, J =
9.7 Hz, 1 H, CH₂COOCH), 5.13 (dd, J = 9.6, 4.6 Hz, 1 H,
CH₃C=CHCH₂), 4.28 (d, J = 9.7 Hz, 1 H, (CH₃)₂CCHOH), 3.71
(s, 1 H, CHOH), 3.47 (bs, 1 H, OH), 3.15 (q, J = 6.8 Hz,
1 H, C(O)CHCH₃), 3.04 (bs, 1 H, OH), 2.68 (s, 3 H,
N=C(CH₃)S), 2.62 (ddd, J = 15.0, 10.2, 10.1 Hz, 1 H,
CH₂CH=CCH₃), 2.45 (dd, J = 14.7, 11.1 Hz, 1 H, CH₂COOCH),
2.38-2.24 (m, 1 H), 2.28 (dd, J = 14.8, 2.2 Hz, CH₂COOCH),
2.22 (d, J = 14.9 Hz, 1 H, CH₂C(CH₃)=CHCH₂), 2.06 (s, 3 H,
CH=CCH₃), 1.90-1.84 (m, 1 H), 1.76-1.69 (m, 1 H), 1.65 (s,
3 H, CH₂C(CH₃)=CH), 1.33 (s, 3 H, C(CH₃)₂), 1.32-1.22 (m,
4 H), 1.19 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 1.06 (s, 3 H,
C(CH₃)₂), 1.00 (d, J = 7.0 Hz, 3 H, CH(CH₃)); ¹³C NMR
(150.9 MHz, CDCl₃) δ 220.4, 170.2, 164.9, 151.8, 139.1,
138.3, 120.8, 119.1, 115.5, 78.9, 74.1, 72.3, 53.6, 41.7,
39.7, 32.6, 31.8, 31.7, 25.4, 23.0, 19.1, 18.1, 16.0.

15.8, 13.5; FAB HRMS (NBA) m/e 492.2795, M + H⁺ calcd for C₂₇H₄₁NO₅ 492.2784.

Synthesis of Dihydroxy Lactone 123 as illustrated in Figure 16. Dihydroxy lactone 123 was prepared from

bis(silylether) lactone 122 (40.0 mg, 0.055 mmol) by treatment with CF₃COOH according to the same procedure described above for the preparation of 70 (Figure 14).

Obtained pure 123 (24.3 mg, 89%): R_f = 0.19 (silica gel, 4% MeOH in Methylene chloride); [α]_D²² -61.0 (c 0.2, CHCl₃); IR (thin film) ν_{max} 3418, 2932, 1731, 1691, 1466, 1381, 1252, 1159, 1067, 1044, 1012, 978, 755 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.99 (s, 1 H, SCH=C), 6.54 (s, 1 H, CH=CCH₃), 5.38 (dd, J = 6.7, 3.8 Hz, 1 H, CH₂COOCH), 5.08 (t, J = 6.9 Hz, 1 H, CH₃C=CHCH₂), 4.32 (dd, J = 10.0, 2.4 Hz, 1 H, (CH₃)₂CCHOH), 3.65 (t, J = 3.4 Hz, 1 H, CHOH), 3.25 (dq, J = 6.7, 3.9 Hz, 1 H, C(O)CHCH₃), 2.68 (s, 3 H, N=C(CH₃)S), 2.55-2.43 (m, 3 H, CH₂COOCH, C(CH₃)=CHCH₂), 2.40 (dd, J = 15.3, 2.5 Hz, 1 H, CH₂COOCH), 2.17-2.10 (m, 1 H, CH₂C(CH₃)=CH), 2.05 (s, 3 H, CH=CCH₃), 1.95 (ddd, J = 13.4, 10.0, 3.3 Hz, 1 H, CH₂C(CH₃)=CH), 1.70-1.57 (m, 3 H), 1.57 (s, 3 H, CH₂C(CH₃)=CH), 1.50-1.35 (m, 2 H), 1.33 (s, 3 H, C(CH₃)₂), 1.15 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 1.03 (s, 3 H, C(CH₃)₂), 0.97 (d, J = 7.0 Hz, 3 H, CH(CH₃)); ¹³C NMR (150.9 MHz, CDCl₃) δ 220.7, 170.7, 165.3, 152.3, 138.5, 137.4, 119.6, 119.4, 115.7, 77.7, 76.2, 71.6, 52.7, 42.7, 39.4, 39.0, 37.3, 30.7, 24.5, 20.5, 19.7, 18.7, 15.9, 15.8, 15.5, 14.3; FAB HRMS (NBA) m/e 492.2772, M + H⁺ calcd for C₂₇H₄₁NO₅ 492.2784.

Synthesis of Epothilone B (2) and its α -epoxide epimer 126 as illustrated in Figure 16. Epoxidation of Lactone 71 . Procedure A: To a solution of lactone 71 (3.0 mg, 6.1 mmol) in benzene (0.2 mL) at -10 °C was added meta-chloroperbenzoic acid (2.9 mg, 50-60% purity, 8.4-10.1 mmol, 1.4-1.6 equiv) and the reaction mixture was stirred at that temperature for 2 h at which time TLC indicated completion of the reaction. The reaction mixture was diluted with EtOAc (5 mL), washed with saturated aqueous NaHCO₃ solution (2 mL), and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic layer was dried (MgSO₄), filtered and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) provided a mixture of epothilone B (2) and its α -epoxy diastereoisomer 124 (2.0 mg, 66%, ca 5:1 ratio by ¹H NMR), which was separated to its components by a second preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) furnishing pure epothilone B (2) (1.6 mg, 52%) as a white solid. Procedure B: To a solution of lactone 71 (5.0 mg, 10.2 mmol) in Methylene chloride (0.5 mL) at -50 °C was added dropwise a solution of dimethyldioxirane in acetone untill the starting material disappeared (TLC). The resulting solution was concentrated, and the crude product was subjected to preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) to give epothilone B (2) and its α -epoxy diastereoisomer 124 in ca 5:1 ratio (3.9 mg, 75%).

Pure epothilone B (2) was obtained (3.1 mg, 60%) by preparative thin layer chromatography as described above. Procedure C: Lactone 71 (3.0 mg, 6.1 mmol) was epoxidised with methyl(trifluoromethyl)dioxirane according to the procedure described above for the epoxidation of 70 (figure 14), to yield a mixture of 2 and its α -epoxy diastereoisomer 124 in ca 5:1 ratio by ^1H NMR (2.6 mg, 85% yield). The major diastereoisomer, epothilone B (2) was isolated as described above (2.1 mg, 69%). 2: Colorless crystals; mp 93 °C (crystallized in Methylene chloride/petroleum ether); R_f = 0.24 (silica gel, 4% MeOH in Methylene chloride); $[\alpha]_{22D}$ -34.3 (c 0.2, MeOH); IR (thin film) ν_{max} 3436, 2954, 2931, 1731, 1684, 1455, 1373, 1290, 1249, 1184, 1143, 1043, 1049, 973, 750 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.97 (s, 1 H, SCH=C), 6.59 (s, 1 H, CH=CCH₃), 5.41 (dd, J = 7.8, 2.8 Hz, 1 H, CH₂COOCH), 4.22 (bs, 2 H, (CH₃)₂CCHOH, OH), 3.77 (dd, J = 4.3, 4.2 Hz, 1 H, CHOH), 3.30 (dq, J = 6.8, 4.1 Hz, 1 H, C(O)CHCH₃), 2.80 (dd, J = 7.6, 4.7 Hz, 1 H, CHOCCH₃), 2.70 (s, 3 H, N=C(CH₃)S), 2.64 (bs, 1 H, OH), 2.54 (dd, J = 14.0, 10.2 Hz, 1 H, CH₂COOCH), 2.36 (d, J = 14.0, 2.9 Hz, 1 H, CH₂COOCH), 2.12 (dd, J = 4.7, 2.8 Hz, 1 H, (CH₃)COCHCH₂CHO), 2.08 (s, 3 H, CH=CCH₃), 1.91 (ddd, J = 15.4, 7.8, 7.6 Hz, 1 H, (CH₃)COCHCH₂CHO), 1.77-1.68 (m, 3 H), 1.53-1.46 (m, 2 H), 1.43-1.37 (m, 2 H), 1.36 (s, 3 H, C(CH₃)OCHCH₂), 1.27 (s, 3 H, C(CH₃)₂), 1.16 (d, J = 6.9 Hz, 3 H, CH(CH₃)), 1.08 (s, 3 H, C(CH₃)₂), 1.00 (d, J = 7.0 Hz, 3 H, CH(CH₃)); ^1H NMR (600 MHz, DMSO- d_6) δ 7.34 (s, 1 H, SCH=C), 6.49 (s, 1 H, CH=CCH₃), 5.27 (dd, J =

9.0, 2.0 Hz, 1 H, CH₂COOCH), 5.07 (d, J = 6.9 Hz, 1 H, OH), 4.45 (bs, 1 H, OH), 4.08 (m, 1 H, (CH₃)₂CCHOH), 3.47 (d, J = 7.4 Hz, 1 H, CHOH), 3.10 (dq, J = 6.8, 6.5 Hz, 1 H, C(O)CHCH₃), 2.81 (dd, J = 9.5, 3.3 Hz, 1 H, CHOCCH₃), 2.64 (s, 3 H, N=C(CH₃)S), 2.40-2.30 (m, 2 H, CH₂COOCH), 2.08 (s, 3 H, CH=CCH₃), 2.05 (ddd, J = 15.0, 2.6, 1.0 Hz, 1 H, (CH₃)COCHCH₂CHO), 1.83 (ddd, J = 15.0, 9.3, 9.1 Hz, 1 H, (CH₃)COCHCH₂CHO), 1.61 (m, 1 H), 1.45-1.35 (m, 3 H), 1.35-1.25 (m, 3 H), 1.17 (s, 6 H, C(CH₃)OCHCH₂, C(CH₃)₂), 1.05 (d, J = 6.6 Hz, 3 H, CH(CH₃)), 0.87 (d, J = 7.0 Hz, 3 H, CH(CH₃)), 0.86 (s, 3 H, C(CH₃)₂); ¹³C NMR (150.9 MHz, DMSO-d₆) δ 218.1, 170.7, 164.8, 152.5, 137.6, 119.5, 118.0, 76.7, 75.7, 70.7, 61.6, 61.1, 53.3, 44.9, 35.6, 33.0, 32.1, 29.6, 23.0, 22.4, 22.0, 19.7, 18.8, 18.4, 16.4, 14.1; FAB HRMS (NBA/CsI) m/e 640.1725, M + Cs⁺ calcd for C₂₇H₄₁NO₆S 640.1709. A natural sample of epothilone B (2) exhibited identical properties to those reported above.

Synthesis of Epothilone 125 and 126 as illustrated in Figure 16. Epoxidation of Lactone 123. Procedure A: Compound 123 (5.0 mg, 10.2 mmol) was epoxidised with mCPBA according to procedure A described above for 2 to yield a mixture of 12S-epi-epothilone B (125) and its α-epoxy-diastereoisomer 126 (3.7 mg, 73% total yield, ca 4:1 by ¹H NMR). Purification by preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) gave pure 12S-epothilone 126 (2.5 mg, 49%) as a white solid. Procedure B: The epoxidation of 123 (3.0 mg, 6.1

mmol) according to the procedure described above for 1 led to epothilones 126 and its α -epoxy diastereoisomer 126 (2.6 mg, 86% total yield, ca 1:1 ratio by ^1H NMR). Preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) furnished pure epothilone 125 (1.3 mg, 43%) and its α -epoxy diastereoisomer 126 (1.3 mg, 43%). 125: R_f = 0.55 (silica gel, 5% MeOH in Methylene chloride); $[\alpha]_{22D}$ -34.5 (c 0.1, CHCl_3); IR (thin film) ν_{max} 3440, 2929, 1731, 1693, 1467, 1384, 1294, 1257, 1151, 1050, 977, 755 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.97 (s, 1 H, SCH=C), 6.60 (s, 1 H, CH=CCH₃), 5.50 (dd, J = 8.0, 4.0 Hz, 1 H, CH₂COOCH), 4.25 (dd, J = 10.1, 3.2 Hz, 1 H, (CH₃)₂CCHOH), 3.80 (bs, 1 H, OH), 3.75 (dd, J = 5.5, 3.6 Hz, 1 H, CHOH), 3.31 (dq, J = 6.7, 6.3 Hz, 1 H, C(O)CHCH₃), 2.88 (dd, J = 6.3, 4.5 Hz, 1 H, CHOCCH₃), 2.69 (s, 3 H, N=C(CH₃)S), 2.59 (bs, 1 H, OH), 2.55 (dd, J = 13.5, 10.4 Hz, 1 H, CH₂COOCH), 2.45 (dd, J = 13.5, 3.7 Hz, 1 H, CH₂COOCH), 2.08 (s, 3 H, CH=CCH₃), 2.05-1.97 (m, 3 H), 1.95-1.90 (m, 1 H, (CH₃)COCHCH₂CHO), 1.75-1.70 (m, 2 H), 1.51-1.45 (m, 3 H), 1.37 (s, 3 H, C(CH₃)OCHCH₂), 1.27 (s, 3 H, C(CH₃)₂), 1.14 (d, J = 6.9 Hz, 3 H, CH(CH₃)), 1.04 (s, 3 H, C(CH₃)₂), 0.95 (d, J = 6.9 Hz, 3 H, CH(CH₃)); ^{13}C NMR (150.9 MHz, CDCl_3) δ 219.6, 170.7, 164.9, 152.1, 136.6, 119.8, 116.4, 77.6, 75.9, 73.3, 61.3, 59.9, 52.9, 44.2, 38.8, 37.2, 36.4, 32.9, 31.3, 21.9, 21.3, 19.8, 19.4, 17.9, 17.4, 14.8; FAB HRMS (NBA/CsI) m/e 640.1686, $M + \text{Cs}^+$ calcd for $\text{C}_{27}\text{H}_{41}\text{NO}_6\text{S}$ 640.1709.

Synthesis of α,β -Unsaturated Ester 127 as

illustrated in Figure 17. A mixture of aldehyde 82 (5.17 g, 15.9 mmol) and stabilized ylide 83 (8.92 g, 24.0 mmol, 1.5 equiv, prepared from 4-bromo-1-butene by: (i) phosphonium salt formation; (ii) anion formation with NaHMDS; and (iii) quenching with MeOC(O)Cl) as described in Murray, R. W.; Jeyaraman, R. J. Org. Chem. 1985, 50, 2847-2853) in benzene (300 mL, 0.05 M) was heated at reflux for 3 h. After cooling to 25 °C, the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 30% ether in hexanes) to afford α,β -unsaturated ester 127 (7.15 g, 95%): R_f = 0.65 (silica gel, 40% ether in hexanes); $[\alpha]_{22D} +10.4$ (c 1.4, CHCl₃); IR (thin film) ν_{max} 2939, 2856, 1715, 1644, 1504, 1464, 1437, 1365, 1284, 1252, 1209, 1076, 955, 836, 776 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.87 (d, J = 7.4 Hz, 1 H, CH=CCOOCH₃), 6.47 (s, 1 H, CH=CCH₃), 5.83-5.71 (m, 1 H, CH=CH₂), 5.01-4.92 (m, 2 H, CH=CH₂), 4.19 (dd, J = 7.7, 4.9 Hz, 1 H, CHOSi), 3.69 (s, 3 H, COOCH₃), 3.05 (d, J = 6.0 Hz, 2 H, CH₂CH=CH₂), 2.67 (s, 3 H, N=C(S)CH₃), 2.46 (ddd, J = 15.1, 7.7, 7.4 Hz, 1 H, CH₂CHOSi), 2.39 (ddd, J = 15.0, 7.5, 5.0 Hz, 1 H, CH₂CHOSi), 1.99 (s, 3 H, CH=CCH₃), 0.86 (s, 9 H, SiC(CH₃)₃), 0.03 (s, 3 H, Si(CH₃)₂), -0.02 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 167.8, 164.4, 152.8, 141.5, 140.6, 135.3, 130.7, 119.1, 115.5, 115.1, 77.6, 51.7, 36.1, 30.9, 25.7, 19.2, 18.1, 13.9, -4.7, -5.1; FAB HRMS (NBA/CsI) m/e 554.1168, M

+ Cs+ calcd for C₂₂H₃₅NO₃SSi 554.1161.

Synthesis of Allylic Alcohol 128 as illustrated in Figure 17. Methyl ester 127 (6.1 g, 14.4 mmol) was dissolved in THF (80 mL) and cooled to -78 °C. DIBAL (44.0 mL, 1 M solution in Methylene chloride, 44.0 mmol, 3.0 equiv) was added dropwise at -78 °C, and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with MeOH (1.0 mL) at -78 °C, and then ether (100 mL) was added, followed by saturated aqueous sodium-potassium tartrate solution (10 mL). The resulting mixture was allowed to warm up to room temperature, where it was stirred for 3 h. The organic layer was separated and the aqueous phase was extracted with ether (2 x 50 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 40 to 80% ether in hexanes) furnished alcohol 128 (5.58 g, 98%): R_f = 0.18 (silica gel, 40% ether in hexanes); [α]_D²⁵ +6.6 (c 1.1, CHCl₃); IR (thin film) ν_{max} 3380, 2928, 2855, 1637, 1505, 1464, 1386, 1253, 1185, 1074, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.88 (s, 1 H, SCH=C), 6.41 (s, 1 H, CH=CCH₃), 5.77-5.69 (m, 1 H, CH=CH₂), 5.48 (dd, J = 7.3, 7.2 Hz, 1 H, CH=CCH₂OH), 5.00 (dd, J = 15.5, 3.3 Hz, 1 H, CH=CH₂), 4.93 (dd, J = 10.0, 3.3 Hz, 1 H, CH=CH₂), 4.12 (dd, J = 6.5, 6.4 Hz, 1 H, CHOSi), 3.97 (s, 2 H, CH₂OH), 2.86-2.76 (m, 2 H, CH₂CH=CH₂), 2.65 (s, 3 H, N=C(S)CH₃), 2.53 (bs, 1 H, OH), 2.36-2.24 (m, 2 H, CH₂CHOSi), 1.94 (s, 3 H, CH=CCH₃), 0.86 (s, 9 H, SiC(CH₃)₃), 0.02 (s, 3 H, Si(CH₃)₂), -0.02

(s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.5, 152.8, 142.0, 138.1, 123.7, 118.7, 115.2, 114.9, 78.3, 66.6, 34.7, 32.4, 25.7, 19.0, 18.1, 13.7, -4.8, -5.0; FAB HRMS (NBA) m/e 394.2232, M + H⁺ calcd for C₂₁H₃₅NO₂SSi 394.2236.

Synthesis of Compound 129 as illustrated in Figure 17. Chlorination of Alcohol 128. Alcohol 128 (3.00 g, 7.60 mmol) was dissolved in CCl₄ (75 mL, 0.1 M) and Ph₃P (4.00 g, 15.2 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 10% ether in hexanes) furnished pure 129 (2.6 g, 83%): R_f = 0.50 (silica gel, 15% ether in hexanes); [α]_D²⁵ +13.7 (c 1.0, CHCl₃); IR (thin film) ν_{max} 2953, 2928, 2855, 1637, 1504, 1470, 1439, 1387, 1254, 1182, 1075, 953, 917, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.93 (s, 1 H, SCH=C), 6.47 (s, 1 H, CH=CCH₃), 5.77-5.69 (m, 1 H, CH=CH₂), 5.66 (dd, J = 7.5, 7.2 Hz, 1 H, CH₂CH=CCH₂Cl), 5.07 (dd, J = 17.1, 1.6 Hz, 1 H, CH=CH₂), 5.02 (dd, J = 10.1, 1.4 Hz, 1 H, CH=CH₂), 4.14 (dd, J = 7.2, 5.5 Hz, 1 H, CHOSi), 4.02 (s, 2 H, CH₂Cl), 2.99-2.89 (m, 2 H, CH₂CH=CH₂), 2.71 (s, 3 H, N=C(S)CH₃), 2.52-2.27 (m, 2 H, CH₂CHOSi), 1.99 (s, 3 H, CH=CCH₃), 0.88 (s, 9 H, SiC(CH₃)₃), 0.05 (s, 3 H, Si(CH₃)₂), 0.00 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.3, 152.9, 141.8, 134.9, 134.7, 128.9, 119.0, 116.2, 115.2, 78.1, 49.9, 35.3, 32.3, 25.8, 19.2, 18.2, 13.9, -4.7, -5.0; FAB HRMS (NBA) m/e 412.1884, M + H⁺

calcd for C₂₁H₃₄ClNOSSi 412.1897.

Synthesis of compound 130 as illustrated in Figure 17. Reduction of 129. Compound 129 (2.60 g, 6.30 mmol) was dissolved in THF (60 mL, 0.1 M) and cooled to 0 °C. LiEt₃BH (12.6 mL, 1.0 M solution in THF, 12.6 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. Aqueous NaOH (1.0 mL, 3.0 N) solution was added followed by addition of Et₂O (150 mL). The organic phase was washed with brine (2 x 20 mL), dried (MgSO₄) and concentrated. Flash column chromatography (silica gel, 20% ether in hexanes) furnished pure 130 (2.38 g, 99%): R_f = 0.60 (silica gel, 15% ether in hexanes); [α]_D²⁵ +17.1 (c 0.7, CHCl₃); IR (thin film) ν_{max} 2928, 2856, 1637, 1505, 1464, 1253, 1181, 1075, 946, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.77-5.68 (m, 1 H, CH=CH₂), 5.22 (dd, J = 7.3, 7.0 Hz, 1 H, CH₂CH=CCH₃), 5.01 (dd, J = 17.1, 3.2 Hz, 1 H, CH=CH₂), 4.96 (dd, J = 10.1, 3.3 Hz, 1 H, CH=CH₂), 4.09 (dd, J = 7.2, 5.9 Hz, 1 H, CHOSi), 2.80 (dd, J = 14.5, 6.5 Hz, 1 H, CH₂CH=CH₂), 2.73-2.68 (m, 1 H, CH₂CH=CH₂), 2.70 (s, 3 H, N=C(S)CH₃), 2.32-2.19 (m, 2 H, CH₂CHOSi), 1.99 (s, 3 H, CH=CCH₃), 1.66 (s, 3 H, CH₂CH=CCH₃), 0.88 (s, 9 H, Si(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.3, 153.2, 142.5, 136.0, 134.4, 122.5, 118.7, 115.1, 114.9, 78.9, 36.6, 35.3, 25.8, 23.5, 19.2, 18.2, 13.9, -4.8, -5.0; FAB HRMS (NBA) m/e 378.2279, M + H⁺ calcd for C₂₁H₃₅NOSSi 378.2287.

Synthesis of Primary Alcohol 131 as illustrated in Figure 17. Selective Hydroboration of Olefinic Compound 130. Compound 130 (1.1 g, 2.91 mmol) was dissolved in THF (3.0 mL, 1.0 M) and the solution was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M solution in THF, 3.5 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH (7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with stirring, followed by H₂O₂ (2.4 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, after which time the reaction mixture was diluted with ether (30 mL). The organic solution was separated and the aqueous phase was extracted with ether (2 x 15 mL). The combined organic layer was washed with brine (2 x 5 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silica gel, 50 to 80% ether in hexanes) furnished primary alcohol 131 (1.0 g, 91%): R_f = 0.17 (silica gel, 50% ether in hexanes); [α]_D +3.6 (c 0.2, CHCl₃); IR (thin film) ν_{max} 3381, 2953, 2929, 2856, 1723, 1660, 1469, 1444, 1376, 1253, 1185, 1073, 941, 837, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H, CH=CCH₃), 5.17 (dd, J = 7.0, 6.9 Hz, 1 H, CH₂CH=CCH₃), 4.11 (dd, J = 7.1, 5.7 Hz, 1 H, CHOSi), 3.59 (dd, J = 6.5, 6.4 Hz, 2 H, CH₂OH), 2.70 (s, 3 H, N=C(Si)CH₃), 2.35-2.28 (m, 1 H, CH₂CHOSi), 2.27-2.20 (m, 1 H, CH₂CHOSi), 2.10 (dd, J = 7.6, 7.5 Hz, 2 H CH₂CH₂CH₂OH), 1.98 (s, 3 H, CH=CCH₃), 1.67 (s, 3 H, CH₂CH=CCH₃), 1.67-1.58 (m, 2 H, CH₂CH₂OH), 0.88 (s, 9 H, Si(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR

(150.9 MHz, CDCl₃) δ 164.5, 153.0, 142.7, 136.2, 122.2, 118.5, 115.0, 78.9, 62.4, 35.4, 30.7, 28.0, 25.8, 23.3, 19.2, 18.3, 14.0, -4.7, -5.0; FAB HRMS (NBA) m/e 396.2382, $M + H^+$ calcd for C₂₁H₃₇NO₂SSi 396.2393.

5

Synthesis of Iodide 81 as illustrated in Figure 17.

Iodide 81 (1.18 g, 92%) was prepared from alcohol 131 (1.0 g, 2.53 mmol) according to the procedure described above for 94 (Figure 12). 81: Colorless oil; R_f = 0.65 (silica gel, 20 % ether in hexanes); $[\alpha]_D^{25} +7.5$ (c 0.8, CHCl₃);

10

IR (thin film) ν_{max} 2955, 2930, 2855, 1504, 1462, 1444, 1376, 1360, 1253, 1183, 1074, 942, 837, 776 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.46 (s, 1 H, CH=CCH₃), 5.20 (dd, J = 7.3, 7.1 Hz, 1 H, CH₂CH=CCH₃),

15

4.09 (dd, J = 7.4, 5.5 Hz, 1 H, CHOSi), 3.14 (dd, J = 7.1, 7.0 Hz, 2 H, CH₂I), 2.69 (s, 3 H, N=C(S)CH₃), 2.34-2.27 (m, 1 H, CH₂CHOSi), 2.26-2.19 (m, 1 H, CH₂CHOSi), 2.17-2.03 (m, 2 H), 2.00 (s, 3 H, CH=CCH₃), 1.93-1.86 (m, 2 H), 1.67 (s, 3 H, CH₂CH=CCH₃) 0.88 (s, 9 H, Si(CH₃)₃), 0.04

20

(s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 164.2, 153.1, 142.3, 134.6, 123.1, 118.6, 115.0, 78.8, 35.4, 32.6, 31.9, 25.8, 23.4, 19.2, 18.2, 14.0, 6.5, -4.7, -5.0; FAB HRMS (NBA) m/e 506.1422, $M + H^+$ calcd for C₂₁H₃₆INOSSi 506.1410.

25

Synthesis of Hydrazone 132 as illustrated in Figure 17. Alkylation of SAMP Hydrazone 80 with Iodide 81. SAMP hydrazone 80 (337 mg, 0.2 mmol, 2.0 equiv; Aldrich) in THF (2.5 mL), was added to a freshly prepared solution of LDA at 0 °C [diisopropylamine (277 mL, 0.20

mmol, 2.0 equiv) was added to n-BuLi (1.39 mL, 1.42 M solution in hexanes, 0.20 mmol, 2.0 equiv) in 2.5 mL of THF at 0 °C] at 0 °C. After stirring at that temperature for 8 h, the resulting yellow solution was cooled to -100 °C, and a solution of iodide 81 (0.5 g, 0.99 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to -20 °C over 10 h, and then poured into saturated aqueous NH₄Cl solution (5 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated. Purification by flash column chromatography on silica gel (20 to 40% ether in hexanes) provided hydrazone 132 (380 mg, 70%, de > 98% by ¹H NMR) as a yellow oil: R_f = 0.17 (silica gel, 20% ether in hexanes); [α]_D²⁵ -27.8 (c 2.6, CHCl₃); IR (thin film) ν_{max} 2931, 2861, 1724, 1653, 1599, 1499, 1451, 1374, 1249, 1178, 1077, 940, 834, 774, 727, 673 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.48 (d, J = 6.6 Hz, 1 H, CNH), 6.44 (s, 1 H, CH=CCH₃), 5.12 (dd, J = 7.1, 6.9 Hz, 1 H, CH₂CH=CCH₃), 4.07 (dd, J = 6.8, 6.2 Hz, 1 H, CHOSi), 3.55 (dd, J = 9.1, 3.7 Hz, 1 H, CH₂OCH₃), 3.41 (dd, J = 9.1, 6.9 Hz, 1 H, CH₂OCH₃), 3.36 (s, 3 H, CH₂OCH₃), 3.35-3.32 (m, 2 H, CH₂N), 2.70 (s, 3 H, N=C(S)CH₃), 2.69-2.62 (m, 1 H), 2.31-2.17 (m, 3 H), 2.04-1.84 (m, 5 H), 1.99 (s, 3 H, CH=CCH₃), 1.79-1.72 (m, 1 H), 1.64 (s, 3 H, CH₂CH=CCH₃) 1.41-1.22 (m, 4 H), 1.01 (d, J = 6.9 Hz, CHCH₃), 0.88 (s, 9 H, SiC(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 164.2, 153.1, 144.3, 142.4, 136.6, 121.5, 118.5, 114.8,

78.9, 74.7, 63.4, 59.1, 50.4, 37.0, 35.3, 35.2, -31.8, 26.4, 25.7, 25.4, 23.3, 22.0, 19.1, 18.9, 18.1, 13.8, -4.8, -5.0; FAB HRMS (NEA) m/e 548.3728, M + H⁺ calcd for C₃₀H₅₃N₃O₂SSi 548.3706.

5

10

15

20

25

Synthesis of Nitrile 66 as illustrated in Figure 17. Monoperoxyphthalic acid magnesium salt (MMPP·6H₂O, 233 mg, 0.38 mmol, 2.5 equiv; Aldrich) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 3.0 mL) at 0 °C. Hydrazone 132 (83 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the mixture was stirred at 0 °C until the reaction was complete by TLC (ca 1 h). The resulting suspension was placed in a separating funnel along with ether (15 mL) and saturated aqueous NaHCO₃ solution (5 mL). The organic layer was separated and the aqueous phase was extracted with ether (10 mL). The combined organic solution was washed with water (5 mL) and brine (5 mL), dried (MgSO₄) and concentrated. Flash column chromatography (silica gel, 50% ether in hexanes) afforded nitrile 133 (53 mg, 80%) as a colorless oil: R_f = 0.44 (silica gel, 50% ether in hexanes); [α]_D²⁵ +10.3 (c 3.2, CHCl₃); IR (thin film) ν_{max} 2926, 2855, 1503, 1457, 1381, 1250, 1179, 1072, 935, 833, 773, cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.92 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.18 (dd, J = 7.0, 6.5 Hz, 1 H, CH₂CH=CCH₃), 4.08 (dd, J = 6.5, 6.0 Hz, 1 H, CHOSi), 2.70 (s, 3 H, N=C(S)CH₃), 2.60-2.53 (m, 1 H), 2.30-2.18 (m, 2 H), 2.11-1.97 (m, 2 H), 1.99 (s, 3 H, CH=CCH₃), 1.67 (s, 3 H, CH₂CH=CCH₃) 1.67-1.45 (m, 4 H), 1.29 (d, J = 6.9

Hz, CHCH₃), 0.88 (s, 9 H, SiC(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDC1₃) δ 164.3, 153.0, 142.3, 135.5, 122.8, 122.4, 118.6, 114.9, 78.4, 35.3, 33.6, 31.1, 25.7, 25.4, 25.1, 23.2, 19.1, 18.1, 17.9, 13.9, -4.8, -5.1; FAB HRMS (NBA) m/e 433.2720, M + H⁺ calcd for C₂₄H₄₀N₂OSSi 433.2709.

Synthesis of Aldehyde 75 as illustrated in Figure 17. Nitrile 133 (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to -78 °C. DIBAL (245 mL, 1 M solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca 1 h). Methanol (150 mL) and aqueous HCl (150 mL, 1 N solution) were sequentially added and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 x 5 mL) and the combined organic solution was washed with brine (5 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 15% ether in hexanes) furnished pure aldehyde 75 (44 mg, 82%): R_f = 0.48 (silica gel, 50% ether in hexanes); [α]_D²² +14.7 (c 1.7, CHCl₃); IR (thin film) ν_{max} 2915, 2859, 1721, 1500, 1455, 1381, 1251, 1183, 1070, 940, 832, 770 cm⁻¹; ¹H NMR (500 MHz, CDC1₃) δ 9.60 (d, J = 1.9 Hz, 1 H, CHO), 6.92 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.16 (dd, J = 7.1, 7.0 Hz, 1 H, CH₂CH=CCH₃), 4.08 (dd, J =

7.0, 5.5 Hz, 1 H, CHOSi), 2.70 (s, 3 H, N=C(S)CH₃), 2.36-
 2.18 (m, 3 H), 2.07-2.01 (m, 2H), 1.99 (s, 3 H, CH=CCH₃),
 1.71-1.64 (m, 1 H), 1.66 (d, J = 1.0 Hz, 3 H, CH₂CH=CCH₃),
 1.43-1.29 (m, 3 H), 1.08 (d, J = 7.0 Hz, 3 H, CH₃CH), 0.88
 5 (s, 9 H, Si(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3
 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 205.0, 164.4,
 153.1, 142.3, 135.9, 122.0, 118.6, 114.9, 78.8, 46.1,
 35.3, 31.7, 30.2, 25.7, 25.1, 23.3, 19.1, 18.2, 13.8,
 13.2, -4.8, -5.1; FAB HRMS (NBA) m/e 436.2717, M + H⁺
 10 calcd for C₂₄H₄₁NO₂SSi 436.2706.

Synthesis of 12Z-Carboxylic Acids 119a and 119b as
 illustrated in Figure 18. Aldol Reaction of Keto Acid
 76 with 12Z-aldehyde 75. A solution of keto acid 76 (365
 15 mg, 1.21 mmol, 1.6 equiv) in THF (5.0 mL) was reacted with
 12Z-aldehyde 75 (330 mg, 0.76 mmol, 1.0 equiv) according
 to the same procedure as described above for the
 condensation of 76 and 75 to afford, after similar
 processing, geometrically pure 12Z-carboxylic acids 119a
 20 (207 mg, 32%) and 119b (181 mg, 28%) and recovered 76.
 12Z-carboxylic acid 119a: R_f = 0.56 (silica gel, 5% MeOH
 in Methylene chloride); [α]_D²² -2.9 (c 0.8, CHCl₃); IR
 (thin film) ν_{max} 2933, 2854, 1708, 1464, 1385, 1249, 1187,
 1079, 983, 830, 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.92
 25 (s, 1 H, SCH=C), 6.58 (s, 1 H, CH=CCH₃), 5.15 (dd, J =
 7.4, 7.1 Hz, 1 H, (CH₃)C=CHCH₂), 4.39 (dd, J = 6.7, 3.0
 Hz, 1 H, (CH₃)₂CCHOSi), 4.11 (dd, J = 7.3, 5.7 Hz, 1 H,
 CH₂CHOSi), 3.74 (dd, J = 6.1, 1.8 Hz, 1 H, CH(CH₃)CHOSi),
 3.13 (dq, J = 7.0, 6.5 Hz, 1 H, C(O)CH(CH₃)), 2.70 (s, 3

H, N=C(CH₃)S), 2.44 (dd, J = 16.4, 3.1 Hz, 1 H, CH₂COOH),
 2.31 (dd, J = 16.4, 6.8 Hz, 1 H, CH₂COOH), 2.28-2.04 (m, 3
 H, CH₂C(CH₃)=CH, CH₂C(CH₃)=CHCH₂), 1.94 (s, 3 H,
 CH=C(CH₃)), 1.96-1.86 (m, 1 H), 1.66 (s, 3 H,
 5 CH₂C(CH₃)=CH), 1.47-1.31 (m, 4 H), 1.17 (s, 3 H, C(CH₃)₂),
 1.12 (s, 3 H, C(CH₃)₂), 1.21-1.09 (m, 1 H), 1.08 (d, J =
 6.8 Hz, 3 H, CH(CH₃)), 0.90-0.85 (m, 30 H, CH(CH₃)), 3 x
 SiC(CH₃)₃), 0.10 (s, 3 H, Si(CH₃)₂), 0.06 (s, 3 H,
 Si(CH₃)₂), 0.05 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H,
 10 Si(CH₃)₂), 0.02 (s, 3 H, Si(CH₃)₂), -0.02 (s, 3 H,
 Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 218.2, 175.5,
 165.0, 152.8, 143.4, 137.0, 121.6, 118.2, 114.5, 79.1,
 73.1, 53.8, 44.4, 40.0, 39.2, 35.3, 32.4, 31.4, 26.2,
 26.0, 25.8, 25.7, 23.5, 23.4, 18.8, 18.7, 18.4, 18.2,
 15 16.8, 15.8, 13.9, -3.9, -4.0, -4.1, -4.6, -4.7, -5.0; FAB
 HRMS (NBA/CsI) m/e 984.4427, M + Cs⁺ calcd for
 C₄₅H₈₅NO₆SSi₃ 984.4460. 12Z-carboxylic acid 119b: R_f =
 0.65 (silica gel, 5% MeOH in Methylene chloride); [α]_D²⁵
 +6.2 (c 0.6, CHCl₃); IR (thin film) ν_{max} 2933, 2854, 1708,
 20 1459, 1386, 1249, 1074, 988, 830, 773 cm⁻¹; ¹H NMR (500
 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H,
 CH=CCH₃), 5.12 (dd, J = 7.4, 6.9 Hz, 1 H, (CH₃)C=CHCH₂),
 4.56 (dd, J = 6.1, 5.6 Hz, 1 H, (CH₃)₂CCHOSi), 4.07 (dd, J
 = 7.6, 5.6 Hz, 1 H, CH₂CHOSi), 3.85 (d, J = 8.4 Hz, 1 H,
 25 CH(CH₃)CHOSi), 3.10 (dq, J = 7.1, 7.0 Hz, 1 H,
 C(O)CH(CH₃)), 2.75 (s, 3 H, N=C(CH₃)S), 2.43-2.10 (m, 4
 H), 1.96-1.88 (m, 2 H), 1.91 (s, 3 H, CH=C(CH₃)), 1.66 (s,
 3 H, CH₂C(CH₃)=CH), 1.35-1.02 (m, 14 H, CH(CH₃)), 2 x CH₂,
 C(CH₃)₂, C(CH₃)₂, CH(CH₃)), 0.92-0.80 (m, 30 H, 3 x

$\text{Si}(\text{CH}_3)_3$, $\text{CH}(\text{CH}_3)$, 0.09-0.01 (m, 18 H, $3 \times \text{Si}(\text{CH}_3)_2$);
 ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.1, 174.2, 165.4, 152.3,
 143.7, 137.1, 121.6, 117.9, 114.4, 78.9, 72.4, 53.8, 45.8,
 40.4, 38.3, 35.6, 35.3, 32.3, 26.7, 26.3, 26.2, 26.0;
 25.8, 25.7, 23.9, 23.3, 18.6, 18.5, 18.4, 17.1, 13.9,
 13.4, -3.4, -3.6, -4.3, -4.6, -4.7, -4.9; FAB HRMS
 (NBA/CsI) m/e 984.4430, $M + \text{Cs}^+$ calcd for $\text{C}_{45}\text{H}_{85}\text{NO}_6\text{SSi}_3$
 984.4460.

Synthesis of 12Z-Hydroxy Acid 73 as illustrated in
 Figure 18. 12Z-carboxylic acid 119a (400 mg, 0.47 mmol)
 was converted to 12Z-hydroxy acid 73 (253 mg, 73% yield)
 according to the same procedure described above for 72
 (Figure 14). 73: Yellow oil; R_f = 0.41 (silica gel, 5%
 MeOH in Methylene chloride); $[\alpha]_{22D} -10.4$ (c 0.4, CHCl_3);
 IR (thin film) ν_{max} 3227, 2933, 2852, 1711, 1696, 1468,
 1387, 1245, 1189, 1087, 986, 834, 773 cm^{-1} ; ^1H NMR (500
 MHz, CDCl_3) δ 6.95 (s, 1 H $\text{SCH}=\text{C}$), 6.67 (s, 1 H,
 $\text{CH}=\text{CCH}_3$), 5.19 (dd, 1 H, J = 7.5, 7.0 Hz, $\text{CH}_3\text{C}=\text{CHCH}_2$),
 4.41 (dd, J = 6.0, 3.5 Hz, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 4.16 (dd, J
 = 6.6, 6.5 Hz, 1 H, CH_2CHOH), 3.78 (d, J = 6.9 Hz, 1 H,
 $\text{CH}(\text{CH}_3)\text{CHOSi}$), 3.13 (dq, J = 6.9, 6.6 Hz, 1 H,
 $\text{C}(\text{O})\text{CHCH}_3$), 2.72 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.47 (dd, J = 16.2,
 3.9 Hz, 1 H, CH_2COOH), 2.40-2.35 (m, 3 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$,
 CH_2COOH), 2.17-2.10 (m, 1 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 2.00 (s, 3 H,
 $\text{CH}=\text{C}(\text{CH}_3)$), 1.99-1.93 (m, 1 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 1.72 (s, 3
 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.53-1.35 (m, 5 H), 1.19 (s, 3 H,
 $\text{C}(\text{CH}_3)_2$), 1.14 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.07 (d, J = 6.7 Hz, 3
 H, $\text{CH}(\text{CH}_3)$), 0.94-0.84 (m, 21 H, $\text{CH}(\text{CH}_3)$, $\text{Si}(\text{CH}_3)_3$), 0.11

(s, 3 H, Si(CH₃)₂), 0.07 (s, 6 H, Si(CH₃)₂), 0.05 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 217.9, 174.8, 165.1, 152.3, 142.1, 139.4, 120.2, 118.5, 115.0, 73.2, 53.8, 44.5, 40.0, 39.1, 34.1, 32.4, 31.2, 26.2, 26.1, 25.9, 23.5, 23.3, 18.9, 18.6, 18.3, 18.1, 16.8, 16.0, 14.6, -3.9, -4.1, -4.2, -4.7; FAB HRMS (NBA/CsI) m/e 870.3632, M + Cs⁺ calcd for C₃₉H₇₁NO₆SSi₂ 870.3595.

Synthesis of Hydroxy Acid 134 as illustrated in Figure 18. 12Z-carboxylic acid 119b (200 mg, 0.24 mmol) was converted to 12Z-hydroxy acid 134 (123 mg, 71% yield) according to the procedure described above for 72 (Figure 14). 134: yellow oil; R_f = 0.45 (silica gel, 5% MeOH in Methylene chloride); [α]_D²⁵ -8.1 (c 0.3, CHCl₃); IR (thin film) ν_{max} 3227, 2933, 2862, 1711, 1691, 1463, 1382, 1250, 1189, 1082, 986, 834, 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.96 (s, 1 H SCH=C), 6.61 (s, 1 H, CH=CCH₃), 5.15 (dd, 1 H, J = 7.5, 7.0 Hz, CH₃C=CHCH₂), 4.55 (dd, J = 6.1, 3.5 Hz, 1 H, (CH₃)₂CCHOSi), 4.12 (dd, J = 8.0, 4.5 Hz, 1 H, CH₂CHOH), 3.86 (d, J = 8.2 Hz, 1 H, CH(CH₃)CHOSi), 3.12 (dq, J = 7.2, 7.0 Hz, 1 H, C(O)CHCH₃), 2.75 (s, 3 H, N=C(CH₃)S), 2.37-2.30 (m, 5 H, CH₂C(CH₃)=CH, CH₂COOH, C(CH₃)=CHCH₂), 1.98 (s, 3 H, CH=C(CH₃)), 1.94-1.89 (m, 1 H), 1.72 (s, 3 H, CH₂C(CH₃)=CH), 1.39-1.04 (m, 14 H, CH(CH₃), CH(CH₃), 2 x CH₂, C(CH₃)₂), 0.95-0.84 (m, 21 H, SiC(CH₃)₃, CH(CH₃)), 0.09 (s, 3 H, Si(CH₃)₂), 0.08 (s, 3 H, Si(CH₃)₂), 0.07 (s, 6 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 218.6, 174.0, 165.6, 152.0, 142.4, 139.4, 120.1, 118.0, 114.7, 72.4, 53.8, 45.8, 40.4, 38.4, 35.5, 34.0, 32.1, 26.4, 26.2, 26.0, 25.9, 23.8, 23.6, 18.5, 18.4,

18.2, 17.2, 14.9, 13.2, -3.5, -3.7, -4.4, -4.8; FAB HRMS (NBA/CsI) m/e 870.3574, M + Cs+ calcd for C₃₉H₇₁NO₆Si₂ 870.3595.

- 5 **Synthesis of Lactone 121 as illustrated in Figure 18.** Macrolactonization of 12Z-hydroxy acid 73. 12Z-hydroxy acid 73 (8.1 mg, 0.011 mmol) was cyclized according to the procedure described above for 73' (Figure 16) to afford lactone 121 (6.1 mg, 77%).
- 10 **Synthesis of Lactone 135 as illustrated in Figure 18.** Macrolactonization of 12Z-Hydroxy Acid 134. The macrolactonization of 12Z-hydroxy acid 134 (5.0 mg, 0.007 mmol) to lactone 135 (3.7 mg, 76%) was carried out according to the procedure described above for 73' (Figure 16). 135: Colorless oil; R_f = 0.83 (silica gel, 2% MeOH in Methylene chloride); [α]_D²⁵ -31.8 (c 0.1, CHCl₃); IR (thin film) ν_{max} 2931, 2860, 1736, 1690, 1461, 1384, 1360, 1296, 1249, 1084, 985, 832, 773 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.98 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.07-5.21 (m, 2 H, CH₃C=CHCH₂, CH₂COOCH), 4.32 (dd, J = 6.8, 5.0 Hz, 1 H, CHOSi), 4.05 (d, J = 5.7 Hz, 1 H, CHOSi), 3.17 (dq, J = 7.0, 6.8 Hz, 1 H, C(O)CHCH₃), 2.70 (s, 3 H, N=C(CH₃)S), 2.57-2.52 (m, 1 H), 2.29 (dd, J = 14.4, 4.6 Hz, 1 H, CH₂COOCH), 2.27-2.13 (m, 1 H), 2.25 (dd, J = 14.5, 7.0 Hz, 1 H, CH₂COO), 2.20-2.15 (m, 1 H), 2.14 (s, 3 H, CH=C(CH₃)), 1.88-1.82 (m, 1 H), 1.57-1.52 (m, 2 H), 1.47-1.38 (m, 3 H), 1.30 (s, 3 H, C(CH₃)₂), 1.11 (d, J = 7.2 Hz, 3 H, CH(CH₃)), 1.08 (s, 3 H, C(CH₃)₂), 0.91 (s, 9 H, SiC(CH₃)₃), 0.89-0.82 (bs, 12 H, SiC(CH₃)₃).
- 25

CH(CH₃)), 0.11 (s, 3 H, Si(CH₃)₂), 0.09 (s, 3 H, Si(CH₃)₂), 0.06 (s, 3 H, Si(CH₃)₂), -0.03 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 220.2, 170.9, 164.8, 153.1, 140.0, 137.6, 120.2, 118.9, 116.3, 79.3, 74.0, 53.3, 48.0, 41.2, 39.7, 34.9, 31.4, 31.3, 26.6, 26.1, 25.9, 25.3, 23.9, 19.0, 18.5, 18.4, 18.1, 16.2, 14.9, 13.8, -3.9, -4.4, -4.6, -4.9; FAB HRMS (NBA/CsI) m/e 852.3451, M + Cs⁺ calcd for C₃₉H₆₉NO₅SSi₂ 852.3489.

Synthesis of Ketone 69 as illustrated in Figure 19. To a solution of aldehyde 87 (1.3 g, 4.53 mmol) in THF (20 mL) at -78 °C was added dropwise lithium tri-tert-butoxyaluminumhydride (4.98 mL, 1.0 M solution in THF, 4.98 mmol, 1.1 equiv). After 5 min, the reaction mixture was brought up to 0 °C and stirred at that temperature for 15 min, before quenching with saturated aqueous solution of sodium-potassium tartrate (25 mL). The aqueous phase was extracted with ether (3 x 20 mL) and the combined organic layer was dried (MgSO₄), filtered and concentrated. The crude primary alcohol so obtained was dissolved in Methylene chloride (25 mL) and cooled to 0 °C. Et₃N (2.5 mL, 15.85 mmol, 3.5 equiv), 4-DMAP (60 mg, 0.09 mmol, 0.02 equiv) and tert-butyldimethylsilyl chloride (2.0 g, 13.59 mmol, 3.0 equiv) were added. The reaction mixture was allowed to stir at 0 °C for 2 h, then at 25 °C for 10 h. MeOH (5 mL) was added and the solvents were removed under reduced pressure. Ether (100 mL) was added followed by saturated aqueous NH₄Cl solution (25 mL) and the organic phase was separated. The aqueous phase was extracted with

ether (2 x 50 mL) and the combined organic solution was dried (MgSO₄), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure

5 bis(silylether) 136 (1.26 g, 70% yield from 20): R_f = 0.67 (silica gel, 20% ether in hexanes); $[\alpha]_{22D}$ -7.3 (c 1.8, CHCl₃); IR (thin film) ν_{max} 2941, 2856, 1701, 1466, 1388, 1252, 1095, 1024, 946, 832, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.06 (dd, J = 8.0, 3.0 Hz, 1 H, CHOSi),

10 3.65-3.56 (m, 2 H, CH₂OSi), 2.56 (dq, J = 18.5, 7.0 Hz, 1 H, CH₂CH₃), 2.46 (dq, J = 18.5, 7.0 Hz, 1 H, CH₂CH₃), 1.56-1.43 (m, 2 H, CH₂CH₂OSi), 1.11 (s, 3 H, C(CH₃)₂), 1.04 (s, 3 H, C(CH₃)₂), 0.98 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 0.88 (s, 9 H, SiC(CH₃)₃), 0.87 (s, 9 H, SiC(CH₃)₃), 0.09

15 (s, 3 H, Si(CH₃)₂), 0.04 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂), 0.02 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 215.5, 73.2, 59.9, 52.9, 37.1, 31.4, 25.9, 25.7, 22.0, 19.8, 18.2, 18.1, 7.6, -4.1, -4.2, -5.4, -5.5; FAB HRMS (NEA) m/e 403.3075, $M + H^+$ calcd for C₂₁H₄₆O₃Si₂ 403.3064.

20

Synthesis of tris(silylethers) 137 and 138 as illustrated in Figure 19.. Aldol Reaction of Ketone 136 with Aldehyde 75. A solution of ketone 136 (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise

25 to a freshly prepared solution of LDA [diisopropylamine (94 mL, 0.67 mmol) was added to n-BuLi (0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of THF at 0 °C] in THF (2.5 mL) at -78 °C. After stirring for 15 min at -

78 °C, the solution was allowed to warm to -40 °C over a period of 1 h. The reaction mixture was cooled to -78 °C, and a solution of aldehyde 8 (244 mg, 0.56 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at -78 °C, and then quenched by dropwise addition of saturated aqueous NH₄Cl solution (2 mL). The aqueous phase was extracted with ether (3 x 5 mL) and the combined organic layer was dried (MgSO₄) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products 137:138 (354 mg (85%) of ca 3:1 by ¹H NMR). Separation of these diastereoisomers was carried out by preparative thin layer chromatography (silica gel, 20% ether in hexanes) leading to pure 137 (270 mg, 64%) and 138 (84 mg, 20%). 137: Colorless oil; R_f = 0.40 (silica gel, 20% ether in hexanes); [α]_D²⁵ -17.5 (c 0.5, CHCl₃); IR (thin film) ν_{max} 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.89 (s, 1 H, SCH=C), 6.44 (s, 1 H, CH=CCH₃), 5.12 (dd, J = 7.1, 7.0 Hz, 1 H, C(CH₃)=CHCH₂), 4.08 (dd, J = 6.8, 6.5 Hz, 1 H, (CH₃)₂CCCHOSi), 3.89 (dd, J = 7.6, 2.7 Hz, 1 H, CH₂CHOSi), 3.69-3.65 (m, 1 H, CH(CH₃)CHOH), 3.59 (t, J = 7.5 Hz, 2 H, CH₂OSi), 3.32-3.27 (m, 1 H, C(O)CH(CH₃)), 2.68 (s, 3 H, N=C(CH₃)S), 2.30-2.19 (m, 2 H, C(CH₃)=CHCH₂), 2.10-1.90 (m, 2 H, CH₂C(CH₃)=CH), 1.98 (s, 3 H, CH=C(CH₃)), 1.65 (s, 3 H, C(CH₃)=CHCH₂), 1.80-1.46 (m, 5 H), 1.34-1.25 (m, 2 H), 1.19 (s, 3 H, C(CH₃)₂), 1.07 (s, 3 H, C(CH₃)₂), 1.01 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 0.89 (s, 18 H, 2 x SiC(CH₃)₃), 0.87 (s, 9 H,

$\text{SiC}(\text{CH}_3)_3$, 0.81 (d, $J = 6.8$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.10 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.08 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.03 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.02 (s, 6 H, $\text{Si}(\text{CH}_3)_2$), -0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 222.0, 164.1, 153.1, 142.4, 136.7, 121.3, 118.5, 114.7, 78.9, 74.7, 74.0, 60.3, 53.8, 41.2, 37.7, 35.9, 32.8, 32.5, 32.2, 26.0, 25.9, 25.8, 25.0, 24.9, 23.5, 22.8, 20.4, 19.0, 18.2, 18.1, 18.0, 15.2, 13.8, 9.5, -3.8, -4.2, -4.8, -5.1, -5.4; FAB HRMS (NBA/CsI) m/e 970.4620, $M + \text{Cs}^+$ calcd for $\text{C}_{45}\text{H}_{87}\text{NO}_5\text{SSi}_3$ 970.4667. 138: Colorless oil; $R_f = 0.33$ (silica gel, 20% ether in hexanes); IR (thin film) ν_{max} 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.90 (s, 1 H, $\text{SCH}=\text{C}$), 6.44 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.16-5.12 (m, 1 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 4.09-4.05 (m, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 3.65-3.58 (m, 3 H, CH_2CHOSi , CH_2OSi), 3.42-3.38 (m, 1 H, $\text{CH}(\text{CH}_3)\text{CHOH}$), 3.24-3.19 (m, 1 H, $\text{C}(\text{O})\text{CH}(\text{CH}_3)$), 2.69 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.31-2.18 (m, 2 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 1.98 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.99-1.88 (m, 2 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.67 (s, 3 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 1.55-1.40 (m, 5 H), 1.35-1.25 (m, 2 H), 1.20 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.13 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.09 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.95 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.88 (s, 18 H, $2 \times \text{SiC}(\text{CH}_3)_3$), 0.87 (s, 9 H, $\text{SiC}(\text{CH}_3)_3$), 0.10 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.04 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.03 (s, 6 H, $\text{Si}(\text{CH}_3)_2$), -0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); FAB HRMS (NBA) m/e 838.5653, $M + \text{Cs}^+$ calcd for $\text{C}_{45}\text{H}_{87}\text{NO}_5\text{SSi}_3$ 838.5691.

Synthesis of tetra(Silylother) 139 as illustrated

in Figure 19.. Compound 137- (275 mg, 0.33 mmol) was dissolved in Methylene chloride (5.0 mL), cooled to 0 °C and treated with 2,6-lutidine (76 mL, 0.66 mmol, 2.0 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (88 mL, 0.39 mmol, 1.2 equiv). After stirring for 2 h at 0 °C, the reaction mixture was quenched with aqueous HCl (5 mL, 1.0 N solution) and the aqueous phase was extracted with Methylene chloride (3 x 5 mL). The combined organic solution was washed with brine (5 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetra(silylether) 139 (300 mg, 96%) as a colorless oil. 139: R_f = 0.56 (silica gel, 10% ether in hexanes); [α]_D²⁵ -10.8 (c 0.5, CHCl₃); IR (thin film) ν_{max} 2919, 2872, 1690, 1461, 1384, 1361, 1249, 1085, 985, 838, 773, 732, 667 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.88 (s, 1 H, SCH=C), 6.43 (s, 1 H, CH=CCH₃), 5.13 (dd, J = 7.1, 7.0 Hz, 1 H, C(CH₃)=CHCH₂), 4.08 (dd, J = 6.8, 6.7 Hz, 1 H, (CH₃)₂CCCHOSi), 3.89 (dd, J = 7.6, 2.7 Hz, 1 H, CH₂CHOSi), 3.77 (dd, J = 6.7, 1.0 Hz, 1 H, CH(CH₃)CHOSi), 3.67-3.62 (m, 1 H, CH₂OSi), 3.58-3.53 (m, 1 H, CH₂OSi), 3.14 (dd, J = 6.8, 6.7 Hz, 1 H, C(O)CH(CH₃)), 2.68 (s, 3 H, N=C(CH₃)S), 2.29-2.17 (m, 2 H, C(CH₃)=CHCH₂), 1.98 (s, 3 H, CH=C(CH₃)), 1.97-1.89 (m, 2 H, CH₂C(CH₃)=CH), 1.64 (s, 3 H, C(CH₃)=CHCH₂), 1.50-1.45 (m, 5 H), 1.34-1.23 (m, 2 H), 1.20 (s, 3 H, C(CH₃)₂), 1.02 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 1.00 (s, 3 H, C(CH₃)₂), 0.88-0.86 (m, 39 H, CH(CH₃)), 4 x SiC(CH₃)₃, 0.08 (s, 3 H, Si(CH₃)₂), 0.07 (s,

3 H, Si(CH₃)₂), 0.04 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂), 0.02 (s, 6 H, Si(CH₃)₂), 0.01 (s, 3 H, Si(CH₃)₂), -0.02 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 218.2, 164.2, 153.2, 142.4, 136.6, 121.5, 118.5, 114.9, 78.8, 77.3, 73.9, 60.9, 53.6, 44.9, 38.8, 37.9, 35.2, 32.4, 30.9, 26.2, 26.1, 25.9, 24.4, 23.4, 19.2, 19.1, 18.5, 18.3, 18.2, 18.1, 17.5, 13.9, -3.7, -3.8, -4.0, -4.7, -4.9, -5.2, -5.3; FAB HRMS (NBA) m/e 952.6515, M + H⁺ calcd for C₅₁H₁₀₁NO₅SSi₄ 952.6556.

Synthesis of Alcohol 140 as illustrated in Figure 19. Alcohol 140 (200 mg, 85%) was obtained from compound 139 (264 mg, 0.28 mmol) according to the procedure described above for 102. 140: Colorless oil; R_f = 0.25 (silica gel, 20% ether in hexanes); [α]_D²² -9.3 (c 0.2, CHCl₃); IR (thin film) ν_{max} 3392, 2939, 2865, 1689, 1463, 1378, 1357, 1252, 1083, 988, 867, 835, 772, 730 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.90 (s, 1 H, SCH=C), 6.44 (s, 1 H, CH=CCH₃), 5.14 (dd, J = 7.0, 6.9 Hz, 1 H, C(CH₃)=CHCH₂), 4.10-4.05 (m, 2 H, (CH₃)₂CCHOSi, CH₂CHOSi), 3.78 (dd, J = 7.0, 1.0 Hz, 1 H, CH(CH₃)CHOSi), 3.63 (t, J = 7.0 Hz, 2 H, CH₂OH), 3.11 (dd, J = 7.0, 6.8 Hz, 1 H, C(O)CH(CH₃)), 2.70 (s, 3 H, N=C(CH₃)S), 2.27-2.19 (m, 2 H, C(CH₃)=CHCH₂), 1.99 (d, J = 1.0 Hz, 3 H, CH=C(CH₃)), 2.10-1.90 (m, 2 H, CH₂C(CH₃)=CH), 1.65 (s, 3 H, C(CH₃)=CHCH₂), 1.50-1.39 (m, 2 H), 1.36-1.29 (m, 3 H), 1.21 (s, 3 H, C(CH₃)₂), 1.20-1.10 (m, 2 H), 1.05 (s, 3 H, C(CH₃)₂), 1.04 (d, J = 6.8 Hz, 3 H, CH(CH₃)), 0.91-0.87 (m, 30 H, CH(CH₃), 3 x SiC(CH₃)₃), 0.11 (s, 3 H, Si(CH₃)₂), 0.07 (s,

3 H, Si(CH₃)₂), 0.06 (s, 6 H, Si(CH₃)₂), -0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 219.5, 164.2, 153.1, 142.4, 136.6, 121.5, 118.5, 114.8, 78.8, 77.4, 72.9, 60.1, 53.6, 45.8, 44.9, 38.6, 38.2, 35.2, 32.4, 30.6, 26.1, 25.9, 24.7, 23.4, 19.1, 18.4, 18.1, 18.0, 17.6, 15.5, 13.8, -3.7, -3.8, -4.0, -4.7, -5.1; FAB HRMS (NBA/CsI) m/e 970.4694, M + Cs⁺ calcd for C₄₅H₈₇NO₅SSi₃ 970.4667.

Synthesis of Aldehyde 141 as illustrated in Figure 19. Oxidation of Alcohol 140. To a solution of oxalyl chloride (54 mL, 0.61 mmol, 2.0 equiv) in Methylene chloride (5.0 mL) was added dropwise DMSO (86 mL, 1.21 mmol, 4.0 equiv) at -78 °C. After stirring for 15 min at -78 °C, a solution of alcohol 73 (255 mg, 0.305 mmol, 1.0 equiv) in Methylene chloride (2.0 mL) was added dropwise at -78 °C over a period of 5 min. The solution was stirred at -78 °C for 30 min, and then Et₃N (250 mL, 1.82 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to 0 °C over a period of 30 min and then ether (20 mL) was added, followed by saturated aqueous NH₄Cl solution (10 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 x 10 mL). The combined organic solution was dried (MgSO₄), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde 141 (241 mg, 95%) as a colorless oil. 141: R_f = 0.47 (silica gel, 20% ether in hexanes); [α]_D²⁵ -12.0 (c 0.1, CHCl₃); IR (thin

film) ν_{max} 2943, 2849, 1725, 1690, 1461, 1384, 1249, 1079, 985, 832, 773 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.74 (m, 1 H, CHO), 6.89 (s, 1 H, SCH=C), 6.43 (s, 1 H, CH=CCH₃), 5.14 (dd, J = 7.1, 7.0 Hz, 1 H, C(CH₃)=CHCH₂), 4.48-4.44 (m, 1 H, (CH₃)₂CCCHOSi), 4.07 (dd, J = 6.1, 5.3 Hz, 1 H, CH₂CHOSi), 3.75 (dd, J = 7.4, 1.0 Hz, 1 H, CH(CH₃)CHOSi), 3.11 (dd, J = 7.0, 6.7 Hz, 1 H, C(O)CH(CH₃)), 2.69 (s, 3 H, N=C(CH₃)S), 2.50 (ddd, J = 16.6, 4.5, 1.0 Hz, 1 H, CH₂CHO), 2.37 (ddd, J = 16.6, 3.2, 1.0 Hz, 1 H, CH₂CHO), 2.28-2.16 (m, 2 H, C(CH₃)=CHCH₂), 1.97 (s, 3 H, CH=C(CH₃)), 1.97-1.89 (m, 2 H, CH₂C(CH₃)=CH), 1.64 (s, 3 H, C(CH₃)=CHCH₂), 1.50-1.25 (m, 5 H), 1.22 (s, 3 H, C(CH₃)₂), 1.05 (s, 3 H, C(CH₃)₂), 1.01 (d, J = 6.9 Hz, 3 H, CH(CH₃)), 0.89-0.84 (m, 30 H, CH(CH₃), 3 x SiC(CH₃)₃), 0.08 (s, 3 H, Si(CH₃)₂), 0.04 (s, 6 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂), 0.02 (s, 3 H, Si(CH₃)₂), -0.02 (s, 3 H, Si(CH₃)₂); ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.5, 201.0, 164.3, 153.2, 142.7, 136.7, 121.5, 118.5, 114.8, 78.9, 77.7, 71.3, 53.4, 45.1, 38.7, 35.3, 32.5, 30.7, 26.2, 25.9, 25.8, 24.1, 23.5, 19.1, 18.7, 18.6, 18.5, 17.7, 15.6, 13.9, -3.6, -3.7, -4.1, -4.5, -4.7, -5.0; FAB HRMS (NBA) m/e 836.5500, $M + H^+$ calcd for C₄₅H₈₅NO₅SSi₃ 836.5535.

Synthesis of Carboxylic Acid 119 as illustrated in Figure 19. Oxidation of Aldehyde 141. Aldehyde 141 (224 mg, 0.29 mmol), *t*BuOH (5.0 mL), isobutylene (5.0 mL, 2 M solution in THF, 10.0 mmol), H₂O (1.0 mL), NaClO₂ (90 mg, 0.86 mmol, 3.0 equiv) and NaH₂PO₄ (60 mg, 0.43 mmol,

1.5 equiv) were combined and stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 6% MeOH in Methylene chloride) to afford carboxylic acid 52 (220 mg, 90%) whose spectroscopic data were identical to those exhibited by 119 obtained above.

Selected physical data for compound 158: ¹H NMR (400 MHz, CDCl₃) δ 6.95 (s, 1 H, ArH), 6.59 (s, 1 H, ArCH=C(CH₃)), 5.44 (ddd, J = 10.5, 10.5, 4.5 Hz, 1 H, CH=CHCH₂), 5.36 (ddd, J = 10.5, 10.5, 5.0 Hz, 1 H, CH=CHCH₂), 5.28 (d, J = 9.4 Hz, 1 H, CO₂CH), 4.23 (d, J = 11.1 Hz, 1 H, (CH₃)₂CCH(OH)), 3.72 (m, 1 H, CHOH(CHCH₃)), 3.43-3.37 (m, 1 H, OH), 3.14 (q, J = 6.7 Hz, 1 H, CH₃CH(C=O)), 3.05 (bs, 1 H, OH), 2.72-2.63 (m, 1 H), 2.69 (s, 3 H, CH₃Ar), 2.48 (dd, J = 14.8, 11.3 Hz, 1 H, CH₂COO), 2.33 (dd, J = 14.8, 2.0 Hz, 1 H, CH₂COO), 2.30-2.13 (m, 2 H) 2.07 (s, 3 H, ArCH=CCH₃), 2.07-1.98 (m, 1 H), 1.80-1.60 (m, 2H), 1.32 (s, 3 H, C(CH₃)₂), 1.36-1.13 (m, 3H), 1.17 (d, J = 6.8 Hz, 3 H, CH₃CH(C=O)), 1.06 (s, 3 H, C(CH₃)₂), 0.99 (d, J = 7.0 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 220.6, 170.4, 165.0 151.9, 138.7, 133.4, 125.0, 119.4, 115.8, 78.4, 74.1, 72.3, 53.3, 41.7, 39.2, 38.5, 32.4, 31.7, 27.6, 27.4, 22.7, 19.0, 18.6, 15.9, 15.5, 13.5; IR (thin film) ν_{max} 3453, 2929, 1733, 1686, 1506, 1464, 1250, 978 cm⁻¹; [α]_D²⁵ -80.2 (c 1.36, CHCl₃); HRMS (FAB), calcd for C₂₆H₃₉CsNO₅S (M + Cs+) 610.1603, found 610.1580.

**Synthesis of of aldehyde 149 as illustrated in
Figure 21**

- 5 Step 1) A solution of (R)-3-bromo-2-methyl-1-propanol
(Aldrich) (6.50 g, 42.4 mmol, 1.0 equiv.) in DMF (30 mL)
at 0 °C was treated with t-butylchlorodimethylsilane (8.23
g, 54.6 mmol, 1.3 equiv.) and imidazole (4.32 g, 63.6
mmol, 1.5 equiv.). After stirring for 90 min at 0 °C, the
10 reaction mixture was diluted with Et₂O (250 mL) and poured
in a 1 M HCl aq. solution (150 mL). The organic phase was
separated, washed with a 1 M HCl aq. solution (2 x 150 mL),
brine (150 mL), dried over MgSO₄ and concentrated in
15 vacuo. Flash chromatography (silica gel, 4% Et₂O in
hexane) afforded 11.2 g (99% yield) of pure compound as a
colorless oil.
- Step 2) A solution of above compound (11.2 g, 42.0 mmol,
1.0 equiv.) in acetone (200 mL) was treated with sodium
iodide (18.9 g, 126 mmol, 3.0 equiv.) and refluxed for 15
20 h. The reaction mixture was then diluted with a 1:1 (v/v)
solution of Et₂O/ hexane (400 mL) and poured in a H₂O (250
mL). The organic phase was separated, washed with brine
(2 x 250 mL), dried over MgSO₄ and concentrated in vacuo.
Flash chromatography (silica gel, 4% Et₂O in hexane)
25 afforded 12.7 g (96% yield) of pure product as a colorless
oil.
- Step 3) A 0.01 M Li₂CuCl₄ solution in THF was prepared by
mixing LiCl (85 mg, 2.0 mmol, 2.0 equiv.) and CuCl₂ (136
mg, 1.0 mmol, 1.0 equiv.) in THF (100 mL). Above compound

made in step 2 (12.7 g, 40.44 mmol, 1.0 equiv.) was dissolved in THF (25 mL), cooled to 0 °C and treated with a solution of 3-butenylmagnesium bromide (0.5 M in THF, 100 mL, 50.0 mmol, 1.25 equiv.), followed by the Li₂CuCl₄ solution (40.0 mL, 0.40 mmol, 0.01 equiv.). The reaction mixture was stirred at 0 °C for 1 h then diluted with Et₂O (500 mL) and poured in a 1 M HCl aq. (250 mL). The organic phase was separated, washed with brine (2 x 250 mL), dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, 4% Et₂O in hexane) afforded 9.3 g (93% yield) of olefin 1003 as a colorless oil.

Step 4) Olefin made in step 3 (4.0 g, 16.4 mmol) was cooled to -78 °C. A gentle stream of ozone was passed through this solution until it turned deep blue. The reaction mixture was then allowed to warm up to room temperature and excess ozone was discharged by sparging argon through the solution. The reaction mixture was then treated with Me₂S (20 mL), Et₃N (10 mL) and MeOH (20 mL). This mixture was stirred at 23 °C for 1 h then diluted with Et₂O (300 mL) and poured in a 1M HCl aq. (250 mL). The organic phase was separated, washed with 1 M HCl aq. (2 x 250 mL), dried over MgSO₄ and concentrated in vacuo. Flash chromatography (silica gel, 8% Et₂O in hexane) afforded 3.9 g (96% yield) of a pure colorless oil of compound 149.

Synthesis of phosphonium resin 147 as illustrated in Figure 21

Step 1) Alkylation of Merrifield Resin: A solution of

1,4-butanediol (7.18 g, 80.0 mmol, 5.0 equiv.) in DMF (600 mL) was cooled to 0 oC and sodium hydride (60 %, 3.20 g, 80.0 mmol, 5.0 equiv.) was added. The reaction mixture was stirred at 0 oC for 2 h and Merrifield resin (40.0 g, 16.0 mmol, 1.0 equiv.) followed by n-Bu4NI (0.58 g, 1.60 mmol, 0.1 equiv.) were added. The reaction mixture was stirred at 23 oC for 20 h, then poured into a frit and the polymer was washed with MeOH (2 x 500 mL), DMF (500 mL), H2O at 80 oC (500 mL), DMF (500 mL), MeOH (500 mL), CH2Cl2 (500 mL), Et2O (2 x 300 mL). The resin was dried under high vaccum to a constant weight of 40.8 g.

Step 2) Conversion of alcohol resin. A suspension of resin from above step 1 (40.8 g, 16.0 mmol, 1.0 equiv.) in CH2Cl2 (700 mL) at 23 oC was treated with Ph3P (20.9 g, 80.0 mmol, 5.0 equiv.), imidazole (6.46 g, 80.0 mmol, 5.0 equiv.) and iodine (16.0 g, 64.0 mmol, 4.0 equiv.). The reaction mixture was stirred at 23 oC for 3 h then poured into a frit and the polymer was washed with CH2Cl2 (500 mL), MeOH (500 mL), CH2Cl2 (500 mL), MeOH (500 mL), CH2Cl2 (500 mL), Et2O (2 x 300 mL). The resin was dried under high vaccum to a constant weight of 42.6 g.

Step 3) Reaction of iodo resin formed in step 2 with Ph3P. A suspension of iodo resin (42.6 g, 16.0 mmol, 1.0 equiv.) in DMF (200 mL) at 23 oC was treated with Ph3P (41.9 g, 160 mmol, 10 equiv.). The reaction mixture was stirred at 90 oC for 12 h then poured into a frit and the polymer was washed with DMF at 80 oC (3 x 500 mL), CH2Cl2 (500 mL), DMF (500 mL), Et2O (3 x 500 mL). The resin was dried under high vaccum to a constant weight of 46.61 g.

Synthesis of Ylide resin 148 as illustrated in Figure 21 Deprotonation of Phosphonium resin 147: A suspension of resin 147 (15.0 g, 5.11 mmol, 1.0 equiv.) in a mixture of DMSO (50 mL) THF (35 mL) at 23 oC was treated with a 1 M solution of NaHMDS in THF (15.3 mL, 15.3 mmol, 3.0 equiv.). The reaction mixture was stirred at 23 oC for 12 h then canulated into a Schlenk frit and the polymer was washed under argon with THF (3 x 100 mL).

Synthesis of resin 150 as illustrated in Figure 21 Wittig reaction of ylide resin 148 with aldehyde 149 (vide supra). A solution of aldehyde 149 (2.50 g, 10.22 mmol, 2.0 equiv.) in THF (25 mL) was cooled at -78 oC and added to the freshly prepared resin 148 (5.11 mmol, 1.0 equiv.) via canula. The resulting suspension was shaken at 23 oC for 3h and the supernatant was filtered off. The polymer was washed with THF (100 mL), MeOH (100 mL), CH₂Cl₂ (100 mL), MeOH (100 mL), CH₂Cl₂ (100 mL), Et₂O (2 x 100 mL). The resin was dried under high vacuum to a constant weight of 14.12 g.

Synthesis of resin 145 as illustrated in Figure 21 Step 1) Desilylation of resin 150 with HF.Pyridine complex. Resin 150 (14.0 g, 5.05 mmol, 1.0 equiv.) was suspended in THF (135 mL) and treated at 0 oC with HF.Pyridine complex (15 mL). The mixture was allowed to warm to 23 oC and shaken for 12 h. The suspension was poured into a frit and the polymer was filtered, washed

with THF (100 mL), CH₂Cl₂ (100 mL), MeOH (100 mL), CH₂Cl₂ (100 mL), Et₂O (2 x 100 mL) and dried under high vacuum to give 13.42 g of deprotected resin.

5 Step 2) Swern oxidation of deprotected resin. To an Oxalyl Chloride (2.56 g, 1.76 mL, 20.0 mmol, 4.0 equiv.) solution in CH₂Cl₂ (50 mL) at -78 °C, was added dropwise DMSO (3.12 g, 2.84 mL, 40.0 mmol, 8.0 equiv.). The solution was stirred at -78 °C for 1 h and cannulated into a suspension of resin (13.26 g, 5.0 mmol, 1.0 equiv.) in CH₂Cl₂,
10 previously cooled to -78 °C. The resulting mixture was stirred for an additional hour and treated with Et₃N (6.25 g, 8.0 mL, 62.5 mmol, 12.5 equiv.), allowed to warm to 23 °C and stirred for 1h. The mixture was filtered and the polymer washed successively with CH₂Cl₂ (250 mL), MeOH
15 (250 mL), CH₂Cl₂ (250 mL), Et₂O (2 x 300 mL), dried under high vacuum to afford 13.25 g of resin 145.

Synthesis of resin 151 as illustrated in Figure 21

20 Step 1) Enolate formation. To a precooled solution of LDA (6.60 mmol, 4.4 equiv.) obtained by treating Diisopropyl amine (0.92 mL, 6.60 mmol, 4.4 equiv.) in THF (25 mL) at 0 °C with n-butyllithium (1.6 M solution in THF, 4.12 mL, 6.60 mmol, 4.4 equiv.) was added a solution of ketoacid
25 144 (vide supra) (0.93 g, 3.0 mmol, 2.0 equiv.) in THF (25 mL) at -78 °C via canula. The solution was allowed to warm to -40 °C and stirred for 1h.

Step 2) Aldol reaction. A suspension of resin 145 (4.0 g, 1.50 mmol, 1.0 equiv.), ZnCl₂ (1.0 M solution in Et₂O, 3.0

mL, 3.0 mmol, 2.0 equiv.) in THF (25 mL), was treated at -78 °C with the enolate solution described above. The suspension was allowed to warm to -40 °C, stirred for 2 h, quenched with saturated NH_4Cl (8 mL) and neutralised at 23 °C with AcOH (0.76 mL, 13.2 mmol, 8.8 equiv). The mixture was poured into a frit, the polymer was washed with THF (100 mL), Et₂O (100 mL), CH_2Cl_2 (100 mL), H₂O (100 mL), MeOH (100 mL), CH_2Cl_2 (100 mL), 1% TFA v/v in CH_2Cl_2 (3x75 mL), CH_2Cl_2 (2x100 mL), Et₂O (2x100 mL) and dried under vacuum to afford 1.96 g of resin 151.

Synthesis of resin 152 as illustrated in Figure 21.
Esterification of resin 151 with alcohol 143. A mixture of resin 151 (1.40 g, 0.46 mmol, 1.0 equiv.), alcohol 143 (vida supra) (0.49 g, 2.31 mmol, 5.0 equiv.), 4-DMAP (0.32 g, 2.31 mmol, 5.0 equiv.) and DCC (0.46 g, 2.31 mmol, 5.0 equiv.) in CH_2Cl_2 (10 mL) was shaken at 23 °C for 15 h. The polymer was filtered, washed with CH_2Cl_2 (2x50 mL), MeOH (2x50 mL), CH_2Cl_2 (2x50 mL), Et₂O (2x50 mL) and dried under vacuum to afford 1.48 g of resin 152.

Synthesis of 154 as illustrated in Figure 21
Metathesis of resin 152. A suspension of resin 152 (500 mg) in CH_2Cl_2 (40 mL) was treated with bis(tricyclohexylphosphine)benzylidene ruthenium dichloride ($\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$) (20 mg) and stirred at 23 °C for 48 h. The polymer was filtered and the filtrate was evaporated and purified by preparative thin layer chromatography (silicagel, 20 % ethyl acetate in hexanes)

to give compounds 154, 155, 156, 157 = ca: 3:3:1:3. 52 % yield from the calculated loading of heterocycle in resin 152.

5 **Synthesis of 157 and 158 as illustrated in Figure 21**

trans-Dihydroxy Lactone 157 and 158. Desilylation of Compound 141 and 155. Silyl ether 141 or 155 (44 mg, 0.074 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)-CH₂Cl₂ (7.4 mL, 0.01 M) to yield, after flash column chromatography (silica gel, 50% EtOAc in hexanes), trans-dihydroxy ester 157 or 158 (33 mg, 93%)

15 **Synthesis of Eposterones 159 and 1 as illustrated in Figure 21.** Epoxidation of cis-Hydroxy Lactone 157 and 158. To a solution of cis-hydroxy lactone 157 and 158 (19 mg, 0.039 mmol) in acetonitrile (390 mL, 0.1 M) is added a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 200 mL, 0.2 M) and the reaction mixture is cooled to 0 °C. Excess of 1,1,1-trifluoroacetone (80 mL, 0.5 M) is added, followed by a portionwise addition of Oxone® (120 mg, 0.20 mmol, 5.0 equiv) and NaHCO₃ (26 mg, 0.31 mmol, 8.0 equiv) with stirring, until the disappearance of starting material is detected by TLC. The reaction mixture is then directly passed through silica gel and eluted with 50% EtOAc in hexanes. Purification by preparative thin layer chromatography (250 mm silica gel plate, 70% EtOAc in

hexanes) provides the diastereomeric eposterones 159 or 1 (epothilone A).

Synthesis of alcohol 163. Allylboration of Aldehyde 162 as illustrated in Figure 25.

Aldehyde 162 (1.0 equiv) was dissolved in anhydrous ether (0.3 M) and the solution was cooled to -100 °C. (+)-Diisopinocampheylallyl borane (1.2 equiv in pentane, prepared from (-)-Ipc₂BOMe and 1.0 equiv of allyl magnesium bromide) was added dropwise under vigorous stirring, and the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol was added at -100 °C, and the reaction mixture was allowed to warm up to room temperature. Amino ethanol (10.0 equiv) was added and stirring was continued for 15 h. The work-up procedure was completed by the addition of saturated aqueous NH₄Cl solution, extraction with EtOAc and drying of the combined organic layers with MgSO₄. Filtration, followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol 163 (91%).

Synthesis of hydroxy Esters 164 and 165. EDC Coupling of Carboxylic Acids 45 and 46 and Alcohol 163 as illustrated in Figure 25. The crude mixture of keto acids 45 and 46 (1.0 equiv; vide supra), 4-(dimethylamino)pyridine (4-DMAP, 1.5 equiv), and alcohol

163 (2.0 equiv) in CH_2Cl_2 (2.0 M) was cooled to 0 °C and then treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 1.5 equiv). The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The work-up procedure was completed by the addition of saturated aqueous NHCO_3 solution, extraction with ether and drying of the combined organic layers with MgSO_4 . Evaporation of the solvents followed by flash column chromatography (silica gel, 15% EtOAc in hexanes) resulted in pure hydroxy esters 164 (49% from keto acid 8) and 165 (33% from keto acid 8).

Synthesis of hydroxy lactones 166 and 167 as illustrated in Figure 26. Cyclization of Diene 164 via Olefin Metathesis. To a solution of diene 164 (1.0 equiv) in CH_2Cl_2 (0.0015 M) was added bis(tricyclohexylphosphine)benzylidene ruthenium dichloride ($\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$, 0.2 equiv) and the reaction mixture was allowed to stir at 25 °C for 20 h. After the completion of the reaction was established by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give hydroxy lactones 166 (40%) and 167 (29%).

Synthesis of cis-Dihydroxy Lactone 168 as illustrated in Figure 26. Desilylation of Compound 166. Silyl ether 166 (1.0 equiv) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid- CH_2Cl_2 (0.01 M) at 0 °C. The reaction mixture was

stirred at 0 °C for 30 min (completion of the reaction by TLC). The work-up procedure was completed by the addition of saturated aqueous NHCO_3 solution, extraction with EtOAc and drying of the combined organic layers with MgSO_4 .

5 Evaporation of the solvents followed by flash column chromatography (silica gel, ether) resulted in pure cis-dihydroxy lactone **168** (89%). $R_f = 0.21$ (silica gel, 50% EtOAc in hexanes); $[\alpha]^{22}_D -46.5$ (c 0.71, CHCl_3); IR (thin film) ν_{max} 3406, 2930, 1733, 1686, 1584, 1251, 733 cm^{-1} ;
 10 ^1H NMR (500 MHz, CDCl_3) δ 7.47 (s, 1 H, ArH), 6.31 (s, 1 H, ArCH=C(CH₃)), 5.43 (ddd, $J = 10.5, 10.5, 4.0$ Hz, 1 H, CH=CHCH₂), 5.36 (ddd, $J = 10.5, 10.5, 4.5$ Hz, 1 H, CH=CHCH₂), 5.28 (d, $J = 9.5$ Hz, 1 H, CO₂CH), 4.15 (d, $J = 11.0$ Hz, 1 H, (CH₃)₂CCH(OH)), 3.72 (m, 1 H, CHOH(CHCH₃)),
 15 3.11 (qd, $J = 7.0, 2.5$ Hz, 1 H, CH₃CH(C=O)), 3.02 (bs, 2 H, OH), 2.70-2.62 (m, 1 H), 2.50 (dd, $J = 15.5, 11.0$ Hz, 1 H, CH₂COO), 2.43 (s, 3 H, CH₃Ar), 2.38 (dd, $J = 15.5, 2.5$ Hz, 1H, CH₂COO), 2.26-2.13 (m, 2 H), 2.07-1.98 (m, 1 H), 1.98 (s, 3 H, ArCH=CCH₃), 1.80-1.60 (m, 2H), 1.31 (s, 3 H, C(CH₃)₂), 1.37-1.13 (m, 3H), 1.17 (d, $J = 7.0$ Hz, 3 H, CH₃CH(C=O)), 1.07 (s, 3 H, C(CH₃)₂), 0.98 (d, $J = 7.0$ Hz, 3 H, CH₃CHCH₂); ^{13}C NMR (150.9 MHz, CDCl_3) δ 220.3, 170.3, 160.9, 137.8, 137.4, 135.6, 133.5, 124.8, 115.9, 78.3, 74.2, 72.6, 53.0, 42.0, 39.0, 38.5, 32.4, 31.6, 27.6, 27.5, 22.5, 19.3, 15.9, 15.6, 13.8, 13.7; HRMS (FAB), calcd for $\text{C}_{26}\text{H}_{40}\text{NO}_6$ ($M + H^+$) 462.2856, found 462.2844.

Synthesis of trans-Dihydroxy Lactone 169.

Desilylation of Compound 167 as illustrated in

Figure 26. Silyl ether 167 (1.0 equiv) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-CH₂Cl₂ (0.01 M) at 0 °C. The reaction mixture was stirred at 0 °C for 60 min (completion of the reaction by TLC). The work-up procedure was completed by the addition of saturated aqueous NHCO₃ solution, extraction with EtOAc and drying of the combined organic layers with MgSO₄.

Evaporation of the solvents followed by flash column chromatography (silica gel, ether) resulted in pure trans-dihydroxy ester 169 (95%). R_f = 0.22 (silica gel, 50% EtOAc in hexanes); [α]_D²² -37.9 (c 0.70; CHCl₃); IR

(film) ν_{max} 3400, 2933, 1733, 1688, 1583, 1466, 1251, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.49 (s, 1 H, ArH), 6.29 (s, 1 H, ArCH=CCH₃), 5.50 (ddd, J = 15.0, 7.5, 7.5 Hz, 1 H, CH=CHCH₂), 5.37 (dd, J = 5.5, 5.5 Hz, 1 H, CO₂CH), 5.34 (ddd, J = 15.0, 7.5, 7.5 Hz, 1 H, CH=CHCH₂), 4.19 (d, J = 10.0, 3.0 Hz, 1 H, (CH₃)₂CCH(OH)), 3.73 (dd, J = 5.5, 2.5 Hz, 1 H, CHOH(CHCH₃)), 3.26 (qd, J = 7.0, 6.5 Hz, 1H, CH₃CH(C=O)), 3.01 (bs, 1 H, OH), 2.86 (bs, 1 H, OH), 2.55 (dd, J = 15.5, 10.0 Hz, 1 H, CH₂COO), 2.49 (dd, J = 15.5, 3.0 Hz, 1 H, CH₂COO), 2.45 (s, 3 H, CH₃Ar), 2.46-2.40 (m, 2 H), 2.23-2.14 (m, 1 H), 2.00-1.92 (m, 1 H), 1.96 (s, 3 H, ArCH=CCH₃), 1.64-1.56 (m, 2 H), 1.47 (dddd, J = 12.5, 12.5, 4.0, 4.0 Hz, 1 H), 1.40-1.00 (m, 2 H), 1.26 (s, 3 H, C(CH₃)₂), 1.18 (d, J = 7.0 Hz, 3 H, CH₃CH(C=O)), 1.06 (s, 3 H, C(CH₃)₂), 0.98 (d, J = 6.5 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 219.9, 170.5, 161.0, 137.4.

136.8, 135.6, 134.5, 125.6, 116.1, 77.2, 76.1, 72.5, 52.3, 43.8, 38.8, 37.6, 36.1, 32.6, 30.3, 27.2, 21.5, 20.4, 16.6, 16.0, 15.1, 13.7; HRMS (FAB), calcd for C₂₆H₄₀NO₆ (M + H⁺) 462.2856, found 462.2866.

5

Synthesis of Hydroxy Lactones 173 and 174 as illustrated in Figure 27. Cyclization of Diene 165 via Olefin Metathesis. To a solution of diene 165 (1.0 equiv) in CH₂Cl₂ (0.0015 M) was added

10

bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (RuCl₂(=CHPh)(PCy₃)₂, 0.2 equiv) and the reaction mixture was allowed to stir at 25 °C for 20 h. After the completion of the reaction was established by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give hydroxy lactones 173 (25%) and 174 (63%).

15

20

Synthesis of cis-Dihydroxy Lactone 175 as illustrated in Figure 27. Desilylation of Compound 173. Silyl ether 173 (1.0 equiv) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-CH₂Cl₂ (0.01 M) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h (completion of the reaction by TLC). The work-up procedure was completed by the addition of saturated aqueous NHCO₃ solution, extraction with EtOAc and drying of the combined organic layers with MgSO₄. Evaporation of the solvents followed by flash column

25

chromatography (silica gel, ether) resulted in pure cis-dihydroxy lactone 175 (75%).

5 Synthesis of trans-Dihydroxy Lactone 176 as
illustrated in Figure 27; Desilylation of
Compound 174. Silyl ether 174 (1.0 equiv) was treated
with a freshly prepared solution of 20% (v/v)
trifluoroacetic acid-CH₂Cl₂ (0.01 M) at 0 °C. The
10 reaction mixture was stirred at 0 °C for 8 h (completion
of the reaction by TLC). The work-up procedure was
completed by the addition of saturated aqueous NHCO₃
solution, extraction with EtOAc and drying of the combined
organic layers with MgSO₄. Evaporation of the solvents
15 followed by flash column chromatography (silica gel,
ether) resulted in pure trans-dihydroxy ester 9 (72%).

20 Synthesis of Epoxalones 161 and 170 as illustrated
in Figure 26; Epoxidation of cis-Hydroxy Lactone
168. To a solution of 168 (1.0 equiv) in acetonitrile
(0.05 M) was added a 0.0004 M aqueous solution of disodium
salt of ethylenediaminetetraacetic acid (Na₂EDTA, 1.0
equiv) and the reaction mixture was cooled to 0 °C. 1,1,1-
Trifluoroacetone (1.0 equiv) was added, followed by a
portionwise addition of Oxone® (10.0 equiv) and NaHCO₃
25 (16.0 equiv) with stirring, until the disappearance of
starting material was detected by TLC. The reaction
mixture was then treated with excess dimethyl sulfide and
immediately purified by flash column chromatography
(silica gel, ether). Further purification by preparative

thin layer chromatography (250 mm silica gel plate, ether) provided epoxide 161 (34%) and a-isomeric epoxide 5 (15%). 161 : R_f = 0.23 (silica gel, Ether); [α]_D = -25.2 (c 0.31, CHCl₃); IR (film) ν_{max} 3417, 2927, 2866, 1731, 1692, 1584, 1260, 756 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) δ = 7.50 (s, 1 H, ArH), 6.35 (s, 1 H, ArCH=CCH₃), 5.44 (dd, 1 H, J = 8.0, 2.5 Hz, CO₂CH), 4.12 (dd, 1 H, J = 10.0, 3.0 Hz, (CH₃)₂CCH(OH)), 3.81 (dd, J = 5.0, 4.0 Hz, 1 H, CHOH(CHCH₃)), 3.66 (bs, 1 H, OH), 3.23 (qd, J = 7.0, 5.5 Hz, 1 H, CH₃CH(C=O)), 3.02 (ddd, J = 7.0, 4.5, 4.5 Hz, 1 H, CH₂CH-O(epoxide)CH), 2.90 (ddd, J = 7.5, 4.0, 4.0 Hz, 1 H, CH₂CH-O(epoxide)CH), 2.54 (dd, J = 14.5, 10.0 Hz, 1 H, CH₂COO), 2.46 (s, 3 H, CH₃Ar), 2.45 (dd, J = 14.5, 3.0 Hz, 1 H, CH₂COO), 2.08 (ddd, J = 15.0, 5.0, 3.0 Hz, 1 H, CH₂CH-O(epoxide)CH), 2.01 (s, 3 H, ArCH=CCH₃), 1.88 (ddd, J = 15.5, 7.5, 7.5 Hz, 1 H, CH₂CH-O(epoxide)CH), 1.78-1.72 (m, 1 H), 1.72-1.65 (m, 1 H), 1.40-1.15 (m, 5 H), 1.36 (s, 3 H, C(CH₃)₂), 1.17 (d, 3 H, J = 7.0 Hz, CH₃CH(C=O)), 1.11 (s, 3 H, C(CH₃)₂), 1.00 (d, J = 6.9 Hz, 3 H, CH₃CHCH₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 220.1, 170.5, 161.0, 137.2, 136.7, 135.9, 116.3, 76.3, 74.9, 73.8, 57.4, 54.3, 52.6, 43.8, 38.7, 36.1, 31.3, 30.4, 26.9, 23.8, 21.4, 21.1, 17.2, 15.8, 14.4, 13.8; HRMS (FAB), calcd for C₂₆H₄₀NO₇ (M + H⁺) 478.2805, found 478.2790.

Synthesis of Epoxalones 171 and 172 as illustrated in Figure 26; Epoxidation of trans-Hydroxy Lactone 169. To a solution of 169 (1.0 equiv) in acetonitrile (0.05 M) was added a 0.0004 M aqueous

5 solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 1.0 equiv) and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (1.0 equiv) was added, followed by a portionwise addition of Oxone® (10.0 equiv) and NaHCO₃ (16.0 equiv) with stirring, until the disappearance of starting material was detected by TLC. The reaction mixture was then treated with excess dimethyl sulfide and immediately purified by flash column chromatography (silica gel, ether). Further purification
10 by preparative thin layer chromatography (250 mm silica gel plate, ether) provided epoxide 171 (25%) and α-isomeric epoxide 172 (20%).

15 **Synthesis of Epoxalones 177 and 178 as illustrated in Figure 27; Epoxidation of cis-Hydroxy Lactone 175.** To a solution of 175 (1.0 equiv) in acetonitrile (0.05 M) was added a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 1.0 equiv) and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (1.0 equiv) was added, followed by a
20 portionwise addition of Oxone® (10.0 equiv) and NaHCO₃ (16.0 equiv) with stirring, until the disappearance of starting material was detected by TLC. The reaction mixture was then treated with excess dimethyl sulfide and immediately purified by flash column chromatography
25 (silica gel, ether). Further purification by preparative thin layer chromatography (250 mm silica gel plate, ether) provided epoxide 177 (38%) and α-isomeric epoxide 178 (17%).

Synthesis of Epoxalones 179 and 180 as illustrated in Figure 27; Epoxidation of trans-Hydroxy Lactone 176. To a solution of 176 (1.0 equiv) in acetonitrile (0.05 M) was added a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 1.0 equiv) and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (1.0 equiv) was added, followed by a portionwise addition of Oxone® (10.0 equiv) and NaHCO₃ (16.0 equiv) with stirring, until the disappearance of starting material was detected by TLC. The reaction mixture was then treated with excess dimethyl sulfide and immediately purified by flash column chromatography (silica gel, ether). Further purification by preparative thin layer chromatography (250 mm silica gel plate, ether) provided epoxide 179 (22%) and α -isomeric epoxide 180 (13%).

Synthesis of *cis*-Bis(TBS) Ether 183 as illustrated in Figure 29 A solution of alcohol 181 (148 mg, 0.32 mmol) and 2,6-lutidine (560 μ l, 4.8 mmol, 15 equiv) in CH₂Cl₂ (3.2 mL, 0.1 M), at 0 °C, is treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 735 μ l, 3.2 mmol, 10 equiv) and stirred at this temperature for 30 minutes, whereupon no starting material is detected by TLC. The reaction mixture is quenched by pouring it into saturated aqueous NH₄Cl (10 mL). Extractions with ether (2 x 10 mL), drying (MgSO₄) and concentration is followed by flash

chromatographic purification (silica gel, 7% EtOAc in hexanes) to provide bis(TBS)ether 183 (182 mg, 99%).

5 **Synthesis of trans-Bis(TBS) Ether 184 as illustrated in Figure 29.** Silylation of Alcohol 182. In accordance with the procedure describing the silylation of alcohol 181, a solution of alcohol 182 (77 mg, 0.17 mmol) and 2,6-lutidine (300 μ L, 2.6 mmol, 15 equiv) in CH_2Cl_2 (1.7 mL, 0.1 M), at 0 °C, is treated with tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 390 μ L, 1.7 mmol, 10
10 equiv) to provide bis(TBS)ether 183 (92 mg, 97%).

Synthesis of cis-Alcohol 185 as illustrated in Figure 29. A solution of TBS ether 183 (182 mg, 0.31 mmol) in MeOH
15 (3.1 mL, 0.1 M) is treated with 10-camphorsulfonic acid (CSA, 72 mg, 0.31 mmol, 1.0 equiv) at room temperature for 12 h, until TLC indicates the disappearance of starting material. The mixture is then poured into into saturated aqueous NaHCO_3 (10 mL), extracted with ether (3 x 10 mL) and dried (MgSO_4).
20 Flash column chromatography (silica gel, 20% EtOAc in hexanes) yields pure 185 (98 mg, 67%).

Synthesis of trans-Alcohol 186 as illustrated in Figure 29. In accordance with the procedure describing the
25 desilylation of TPS ether 183, a solution of TPS ether 184 (31 mg, 0.05 mmol) in methanol (1.6 mL, 0.1 M) was treated with 10-camphorsulfonic acid (CSA, 37 mg, 0.16 mmol, 1.0 equiv) to yield diol 186 (51 mg, 69%) as a crystalline solid.

Synthesis of Carboxylic acid 187 as illustrated in Figure 29 Ethyl bromopyruvate (1.66 mL, 13.2 mmol, 1 equiv) and thioacetamide (1.05 g, 13.9 mmol, 1.05 equiv) are dissolved in 95% aqueous ethanol (14 mL, 1 M)- and heated at reflux for 5 minutes. Completion of the reaction is indicated by TLC. The reaction mixture is then cooled to room temperature, concentrated in vacuo, suspended in CHCl₃ (20 mL) and washed with saturated aqueous NaHCO₃ (2 x 20 mL) and with H₂O (20 mL). Drying (MgSO₄) and concentration is followed by flash chromatographic purification (silica gel, EtOAc) to yield the corresponding ethyl ester of acid 7 (2.26 g, 100%). This ester is dissolved in THF-H₂O (1:1; 14 mL, 1 M) and submitted to the action of lithium hydroxide (1.66 g, 39.6 mmol, 3.0 equiv). After stirring at room temperature for 45 min TLC indicates the disappearance of starting material. The mixture is poured into H₂O (20 mL) and extracted with ether (2 x 20 mL). Acidification to pH ~ 2 to 3 with aqueous 4 N HCl is followed by extractions with EtOAc (6 x 20 mL). Drying (MgSO₄) and concentration gives pure carboxylic acid 187 (1.36 g, 72%).

Synthesis of cis-Keto Ester 188 as illustrated in Figure 29. EDC Coupling of Alcohol 185 with Thiazole Acid 187. A suspension of thiazole acid 187 (54 mg, 0.38 mmol, 2.0 equiv), 4-(dimethylamino)pyridine (4-DMAP, 2.3 mg, 0.019 mmol, 0.1 equiv) and alcohol 185 (88 mg, 0.19 mmol, 1.0 equiv) in CH₂Cl₂ (3.8 mL, 0.05 M) is cooled to 0 °C and then treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 109 mg, 0.57 mmol, 3.0 equiv). The

reaction mixture is stirred at 0 °C for 2 h and then at 25 °C for 12 h, until TLC indicates completion of the reaction. The solution is separated between EtOAc (10 mL) and water (10 mL). The aqueous layer is extracted with EtOAc (2 x 10 mL) and dried (MgSO₄). Evaporation of the solvents is followed by flash column chromatography (silica gel, 30% EtOAc in hexanes) results in pure keto ester 188 (102 mg, 92%).

Synthesis of trans-Keto Ester 189 as illustrated in Figure 29. By analogy to the procedure described above for the synthesis of keto ester 188, a solution of thiazole acid 187 (28 mg, 0.198 mmol, 2.0 equiv), 4-dimethylaminopyridine (4-DMAP, 1.2 mg, 0.0099 mmol, 0.1 equiv), and alcohol 186 (46 mg, 0.099 mmol, 1.0 equiv) in CH₂Cl₂ (2.0 mL) is treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 57 mg, 0.297 mmol, 3.0 equiv) to provide, after flash column chromatography (silica gel, 20% EtOAc in hexanes), keto ester 189 (49 mg, 84%).

Synthesis of cis-Hydroxy Lactone 190 as illustrated in Figure 29. Silyl ether 188 (95 mg, 0.16 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-CH₂Cl₂ (16 mL, 0.01 M) at 0 °C. The reaction mixture was stirred at 0 °C for 45 min (completion of the reaction by TLC), and then poured into saturated aqueous NaHCO₃ (50 mL), extracted with EtOAc (3 x 20 mL), dried over MgSO₄ and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica

gel, 50% EtOAc in hexanes) to obtain cis-hydroxy lactone 190 (74 mg, 96%).

5 **Synthesis of trans-Dihydroxy Lactone 191 as**
illustrated in Figure 29. Silyl ether 189 (44 mg, 0.074 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)-CH₂Cl₂ (7.4 mL, 0.01 M), according to the procedure described for cis-dihydroxy lactone 8, to yield, after flash column chromatography
10 (silica gel, 50% EtOAc in hexanes), trans-dihydroxy ester 191 (33 mg, 93%)

Synthesis of Eposterones 192 and 194 as illustrated in
Figure 29. To a solution of cis-hydroxy lactone 190 (19 mg, 0.039 mmol) in acetonitrile (390 mL, 0.1 M) is added a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 200 mL, 0.2 M) and the reaction mixture is cooled to 0 °C. Excess of 1,1,1-trifluoroacetone (80 mL, 0.5 M) is added, followed by a
15 portionwise addition of Oxone® (120 mg, 0.20 mmol, 5.0 equiv) and NaHCO₃ (26 mg, 0.31 mmol, 8.0 equiv) with stirring, until the disappearance of starting material is detected by TLC.
20 The reaction mixture is then directly passed through silica gel and eluted with 50% EtOAc in hexanes. Purification by
25 preparative thin layer chromatography (250 mm silica gel plate, 70% EtOAc in hexanes) provides the diastereomeric eposterones 192 (9.5 mg, 48%) and 194 (3.4 mg, 17%).

Synthesis of Eposterones 193 and 195 as illustrated in Figure 29. As described for the epoxidation of cis-hydroxy lactone 190, trans-hydroxy lactone 191 (22 mg, 0.046 mmol) in MeCN (460 mL, 0.1 M) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na₂EDTA, 230 mL, 0.2 M), 1,1,1-trifluoroacetone (92 mL, 0.5 M), Oxone® (141 mg, 0.23 mmol, 5.0 equiv) and NaHCO₃ (31 mg, 0.37 mmol, 8.0 equiv), to yield, after purification by preparative thin layer chromatography (250 mm silica gel plate, ether), eposterones 193 (7.3 mg, 32%) and 195 (5.2 mg, 23%).

Synthesis of Eposterones 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209 and 210 as illustrated in Figure 30. By simple modification of the esterification step, i.e. replacing the thiazole carboxylic acid 187 in Figure 29 with the known carboxylic acids found in epoxalone (198), eleutherobin (197) and taxol (196), other members of the eposterone family can be created including the various isomers: 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209 and 210.

Aldehyde 212. Reduction of Ester 211 as illustrated in Figure 31. Ethyl ester 211 (52.5 g, 0.306 mol) was dissolved in CH₂Cl₂ (1 L, 0.3 M) and cooled to -78 °C. DIBAL (490.0 mL, 1 M solution in CH₂Cl₂, 0.4896 mol, 1.6 equiv) was added dropwise via a cannula while the temperature of the reaction mixture was maintained at -78 °C. After the addition was complete, the reaction mixture was stirred at the same

temperature until its completion was verified by TLC (ca 1 h). Methanol (100 mL) was added at -78 °C and was followed by addition of EtOAc (1 L) and saturated aqueous NH_4Cl solution (300 mL). The quenched reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic phase was dried over MgSO_4 , filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 Å 90% ether in hexanes) furnished the desired aldehyde 212 (33.6 g, 90%):

Synthesis of Aldehyde 213 as illustrated in Figure 31. Aromatic aldehyde 212 (31.1 g, 0.245 mol) was dissolved in benzene (500 mL) and 2-(triphenylphosphoranilidene)-propionaldehyde (90.0 g, 0.282 mol, 1.15 equiv) was added. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (ca 2 h). Evaporation of the solvent under reduced pressure, followed by flash column chromatography (10 Å 90% ether in hexanes) produced the desired aldehyde 213 (40.08 g, 98%):

Synthesis of Alcohol 214. Allylboration of Aldehyde 213 as illustrated in Figure 31. Aldehyde 213 (20.0 g, 0.120 mol) was dissolved in anhydrous ether (400 mL) and the solution was cooled to -100 °C. (+)-Diisopinocampheylallyl borane (1.5 equiv in pentane, prepared from 60.0 g of (-)-Ipc2BOMe and 1.0 equiv of allyl magnesium bromide according to the method described for the synthesis the corresponding thiazole), was added dropwise under vigorous stirring, and

the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol (40 mL) was added at -100 °C, and the reaction mixture was allowed to warm up to room temperature. Amino ethanol (72.43 mL, 1.2 mol, 10.0 equiv) was added and stirring was continued for 15 h. The work-up procedure was completed by the addition of saturated aqueous NH₄Cl solution (200 mL), extraction with EtOAc (4 x 100 mL) and drying of the combined organic layers with MgSO₄. Filtration, followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol 214 (24.09 g, 96%):

Synthesis of Compound 5. Silylation of Alcohol 214 as illustrated in Figure 31. Alcohol 214 (7.0 g, 0.033 mol) was dissolved in DMF (35 mL, 1.0 M), the solution was cooled to 0 °C and imidazole (3.5 g, 0.050 mol, 1.5 equiv) was added. After stirring for 5 min, tert-butyldimethylsilyl chloride (6.02 g, 0.040 mol, 1.2 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 45 min, and then at 25 °C for 2.5 h; after which time no starting alcohol was detected by TLC. Methanol (2 mL) was added at 0 °C and the solvent was removed under reduced pressure. Ether (100 mL) was added, followed by saturated aqueous NH₄Cl solution (20 mL), the organic phase was separated and the aqueous phase was extracted with ether (2 x 20 mL). The combined organic solution was dried (MgSO₄), filtered over celite and the solvents were removed under

reduced pressure. Flash column chromatography (silica gel, 10 & 20% ether in hexanes) provided pure 215 (10.8 g, 99%).

Synthesis of Aldehyde 217 as illustrated in Figure

5 31.. Dihydroxylation of Olefin 215 and 1,2 Glycol Cleavage of diol 216. Olefin 215 (16.7 g, 51.6 mmol) was dissolved in THF/tBuOH (1 : 1, 500 mL) and H₂O (50 mL). 4-Methylmorpholine N-oxide (NMO) (7.3 g, 61.9 mmol, 1.2 equiv) was added at 0 °C, followed by OsO₄ (5.2 mL, solution in tBuOH 1.0 mol%, 2.5% by weight). The mixture was vigorously stirred for 2.5 h
10 at 0 °C and then for 12 h at 25 °C. After completion of the reaction, Na₂SO₃ (5.0 g) was added at 0 °C, followed by H₂O (100 mL). Stirring was continued for another 30 min and then ether (1 L) was added, followed by saturated aqueous NaCl
15 solution (2 x 100 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 x 100 mL). The combined organic extracts were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, ether & EtOAc) provided
20 17.54 g (95%) of the expected 1,2-diol 216 as a 1:1 mixture of diastereoisomers:

The diol obtained from 215 as described above (5.2 g, 14.5 mmol) was dissolved in EtOAc (150 mL) and cooled to 0 °C. Pb(OAc)₄ (8.1 g, 95% purity, 18.3 mmol, 1.2 equiv) was then
25 added portionwise over 10 min, and the mixture was vigorously stirred for 15 min at 0 °C. After completion of the reaction, the mixture was filtered through silica gel and washed with 60% ether in hexanes. The solvents were then

removed under reduced pressure providing pure aldehyde 217 (4.7 g, 98%):

Synthesis of Alcohol 218 as illustrated in Figure 31.

- 5 Reduction of Aldehyde 217. A solution of aldehyde 215 (440 mg, 1.35 mmol) in MeOH (13 mL) was treated with NaBH₄ (74 mg, 2.0 mmol, 1.5 equiv) at 0 °C for 15 min. The solution was diluted with ether (100 mL) and then saturated aqueous NH₄Cl solution (5 mL) was carefully added. The organic phase was
10 washed with brine (10 mL), dried (MgSO₄) and concentrated. Flash column chromatography (silica gel, 60% ether in hexanes) gave alcohol 218 (425 mg, 96%) as a colorless oil.

Synthesis of Iodide 219 as illustrated in Figure 31.

- 15 Iodination of Alcohol 218. A solution of alcohol 218 (14.0 g, 42.7 mmol) in ether: MeCN (3:1, 250 mL) was cooled to 0 °C. Imidazole (8.7 g, 128.1 mmol, 3.0 equiv), Ph₃P (16.8 g, 64.1 mmol, 1.5 equiv), and iodine (16.3 g, 64.1 mmol, 1.5 equiv) were sequentially added and the mixture was stirred
20 for 0.5 h at 0 °C. A saturated aqueous solution of Na₂S₂O₃ (50 mL) was added, followed by the addition of ether (600 mL). The organic phase was washed with brine (50 mL), dried (MgSO₄), and the solvents were removed under vacuum. Flash column chromatography (silica gel, 15% ether in hexanes) gave
25 pure iodide 219 (16.6 g, 89%) as a colorless oil:

Synthesis of Phosphonium Salt 220 as illustrated in Figure 31. A mixture of iodide 219 (16.5g, 37.7 mmol) and Ph₃P (10.9 g, 41.5 mmol, 1.1 equiv) was heated neat at 100 °C

for 2 h. Purification by flash column chromatography (silica gel, CH₂Cl₂; then 7% MeOH in CH₂Cl₂) provided phosphonium salt 220 (25.9 g, 98%) as a white solid.

5 **Synthesis of Olefinic Compound 222 as illustrated in Figure 32.** Phosphonium salt 220 (9.0 g, 12.93 mmol, 1.5 equiv) was dissolved in THF (90 mL) and the solution was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M solution in THF, 12.84 mL, 12.84 mmol, 1.48 equiv) was
10 slowly added and the resulting mixture was stirred at 0 °C for 15 min. The reaction mixture was then cooled to -20 °C before ketone 221 (2.23 g, 8.62 mmol, 1.0 equiv) in THF (10 mL) was added and the reaction mixture was stirred at the same temperature for 12 h. Saturated aqueous NH₄Cl solution
15 (50 mL) was added and the mixture was extracted with ether (200 mL). The organic phase was washed with brine (2 x 100 mL), dried (MgSO₄) and concentrated to afford, after flash column chromatography (silica gel, 2% ether in hexanes) olefins 222 (3.8g, 73%, Z:E ca. 1:1 by ¹H NMR).

20 **Synthesis of Hydroxy Olefins 223 as illustrated in Figure 32.** Desilylation of Silylether 222. Silylether 222 (3.80 g, 6.88 mmol) was dissolved in CH₂Cl₂ : MeOH (1:1, 70 mL) and the solution was cooled to 0 °C prior to addition of
25 CSA (1.68 g, 7.23 mmol, 1.05 equiv) during a 5 min period. The resulting mixture was stirred for 30 min at 0 °C, and then for 1 h at 25 °C. Et₃N (1.57 mL, 7.23 mmol, 1.05 equiv) was added, and the solvents were removed under reduced

pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished pure hydroxy compound 223 (2.9 g, 97%).

Synthesis of Aldehyde 224 as illustrated in Figure 32

5 Oxidation of Alcohol 223. Alcohol 223 (mixtures of Z and E geometrical isomers, 4.60 g, 10.64 mmol) was dissolved in CH₂Cl₂ (105 mL, 0.1 M). DMSO (35 mL), Et₃N (7.4 mL, 53.20 mmol, 5.0 equiv) and SO₃·pyr (3.4 g, 21.28 mmol, 2.0 equiv) were added at 25 °C and the resulting mixture was stirred for
10 30 min. Saturated aqueous NH₄Cl solution (50 mL) and ether (300 mL) were added, and the organic phase was separated and washed with brine (2 x 30 mL), dried (MgSO₄), and concentrated under reduced pressure. Flash column chromatography (silica gel, 20% ether in hexanes) furnished
15 aldehyde 224 (4.40 g, mixture of Z:E isomers, ca 1:1, 95%).

Synthesis of tris(Silylethers) 226 and 227 as illustrated in Figure 32.

Aldol Reaction of Keto Acid 225 with Aldehyde 224. A solution of keto acid 225 (1.52 g, 5.10 mmol, 1.2 equiv) in THF (10 mL) was added dropwise to a
20 freshly prepared solution of LDA [diisopropylamine (1.78 mL, 12.78 mmol) was added to n-BuLi (7.95 mL, 1.6 M solution in hexanes, 12.78 mmol) in 20 mL of THF at 0 °C] at -78 °C. After stirring for 15 min, the solution was allowed to warm
25 to -40 °C, and after 0.5 h at that temperature it was recooled to -78 °C. A solution of aldehyde 224 (1.79 g, 4.24 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred for 15 min, and then quenched at -78 °C by slow addition of saturated aqueous NH₄Cl solution (20 mL). The

reaction mixture was warmed to 0 °C, and AcOH (2.03 mL, 26.84 mmol, 6.3 equiv) was added, followed by addition of EtOAc (50 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined
5 organic solution was dried over MgSO₄ and concentrated under vacuum to afford a mixture of aldol products in a ca 1:1 ratio (1H NMR) and unreacted keto acid 225. The mixture was dissolved in CH₂Cl₂ (50 mL) and treated, at 0 °C, with 2,6-lutidine (3.2 mL, 27.36 mmol) and tert-butyldimethylsilyl
10 trifluoromethanesulfonate (4.2 mL, 18.24 mmol). After stirring for 2 h (complete reaction by TLC), aqueous HCl (20 mL, 10% solution) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic solution was
15 washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure to give a mixture of the tetra-tert-butyldimethylsilyl ethers. The crude product was dissolved in MeOH (50 mL) and K₂CO₃ (1.40 g, 10.20 mmol) was added at 25 °C. The reaction mixture was vigorously stirred for 15
20 min, and then filtered. The residue was washed with MeOH (20 mL) and the solution was acidified with ion exchange resin (DOWEX 50WX8-200) to pH 4-5, and filtered again. The solvent was removed under reduced pressure and the resulting residue was dissolved in EtOAc (50 mL) and washed with saturated
25 aqueous NH₄Cl solution (50 mL). The aqueous phase was extracted with EtOAc (4 x 25 mL) and the combined organic solution was dried (MgSO₄), filtered and concentrated to furnish a mixture of carboxylic acids 226, 227 and 225. Purification by preparative thin layer chromatography (silica

gel, 5% MeOH in CH₂Cl₂), gave pure acids 226 (1.1 g, 31% from 224) and 227 (1.0 g, 30% from 224) as colorless oils.

Synthesis of Hydroxy Acid 228 as illustrated in Figure 32. Selective Desilylation of 226. A solution of tris(silyl) ether 226 (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (10 mL), dried (MgSO₄) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH₂Cl₂) to provide hydroxy acid 228 (203 mg, 78%) as a yellow oil.

Synthesis of Lactones 230 and 229 as illustrated in Figure 33. A solution of hydroxy acid 228 (140 mg, mixture of Z and E isomers, ca 1:1, 0.189 mmol) in THF (2.6 mL) was treated at 0 °C with Et₃N (58 mL, 0.416 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (29.4 mL, 0.246 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added to a solution of 4-DMAP (233 mg, 1.896 mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 °C and stirred at that temperature for 10 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by preparative thin layer chromatography (silica gel, 5% MeOH in CH₂Cl₂), gave pure

lactones 230 (50 mg, 37%) and 229 (54 mg, 40%) as colorless oils.

5 **Synthesis of Dihydroxy lactone 232 as illustrated in Figure 33.** To lactone 230 (50 mg, 0.071 mmol), cooled to -20 °C, was added a freshly prepared 20% (v/v) CF₃COOH solution in CH₂Cl₂ (400 mL). The reaction mixture was allowed to reach 0 °C and was stirred for 1 h at that temperature. The solvents were evaporated under reduced pressure and the crude
10 product was purified by preparative thin layer chromatography (silica gel, 6% MeOH in CH₂Cl₂) to afford pure dihydroxy lactone 232 (31 mg, 92%).

15 **Synthesis of Dihydroxy Lactone 231 as illustrated in Figure 33.** Dihydroxy lactone 231 was prepared from bis(silylether) lactone 229 (40.0 mg, 0.055 mmol) by treatment with CF₃COOH according to the same procedure described above for the preparation of 232. Obtained pure
20 231 (24.3 mg, 89%).

20 **Synthesis of Compound 235 and its α-epoxide epimer 236 as illustrated in Figure 33.** Procedure A: To a solution of lactone 232 (3.0 mg, 6.1 mmol) in benzene (0.2 mL) at -10 °C was added meta-chloroperbenzoic acid (2.9 mg, 50-60%
25 purity, 8.4-10.1 mmol, 1.4-1.6 equiv) and the reaction mixture was stirred at that temperature for 2 h at which time TLC indicated completion of the reaction. The reaction mixture was diluted with EtOAc (5 mL), washed with saturated aqueous NaHCO₃ solution (2 mL), and the aqueous phase was

extracted with EtOAc (3 x 2 mL). The combined organic layer was dried (MgSO₄), filtered and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in CH₂Cl₂) provided a mixture of 235 and its a-epoxy diastereoisomer 236 (2.0 mg, 66%, ca 5:1 ratio by ¹H NMR), which was separated to its components by a second preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) furnishing pure 235 (1.6 mg, 52%) as a white solid. Procedure B: To a solution of lactone 232 (5.0 mg, 10.2 mmol) in CH₂Cl₂ (0.5 mL) at -50 °C was added dropwise a solution of dimethyldioxirane in acetone until the starting material disappeared (TLC). The resulting solution was concentrated, and the crude product was subjected to preparative thin layer chromatography (silica gel, 5% MeOH in CH₂Cl₂) to give 235 and its a-epoxy diastereoisomer 236 in ca 5:1 ratio (3.9 mg, 75%). Pure 235 was obtained (3.1 mg, 60%) by preparative thin layer chromatography as described above. Procedure C: To a solution of 232 (10 mg, 21.0 mmol) in MeCN (200 mL) was added 4.10⁻⁴ M aqueous solution of disodium ethylenediaminetetraacetate (Na₂EDTA, 120 mL) and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (200 mL) was added followed by a mixture of Oxone® (61 mg, 0.10 mmol, 5.0 equiv) and NaHCO₃ (14.0 mg, 0.17 mmol, 8.0 equiv) with stirring until completion of the reaction was revealed by TLC. The reaction mixture was treated with excess Me₂S (100 mL) and water (500 mL) and was then extracted with EtOAc (4 x 2 mL). The combined organic phase was dried (MgSO₄), filtered, and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in

CH₂Cl₂) gave a mixture of 235 and its α -epoxide epimer 236 (8.6 mg, 78% total yield). A second preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) furnished pure 235 (6.4 mg, 65%) as a white solid.

5

Synthesis of Epothilone 23 and 24 as illustrated in Figure 33. Procedure A: Compound 231 (5.0 mg, 10.2 mmol) was epoxidised with mCPBA according to procedure A described above for 232 to yield a mixture of 234 and its α -epoxy-diastereoisomer 233 (3.7 mg, 73% total yield, ca 4:1 by ¹H NMR). Procedure B: The epoxidation of 231 (3.0 mg, 6.1 mmol) according to the procedure described above for 232 led to epothilones 233 and its α -epoxy diastereoisomer 234 (2.6 mg, 86% total yield, ca 1:1 ratio by ¹H NMR).

15

Synthesis of α,β -Unsaturated Ester 237 as illustrated in Figure 34. A mixture of aldehyde 217 (5.17 g, 15.9 mmol) and stabilized ylide (8.92 g, 24.0 mmol, 1.5 equiv, prepared from 4-bromo-1-butene by: (i) phosphonium salt formation; (ii) anion formation with NaHMDS; and (iii) quenching with MeOC(O)Cl₂) in benzene (300 mL, 0.05 M) was heated at reflux for 3 h. After cooling to 25 °C, the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 30% ether in hexanes) to afford α,β -unsaturated ester 237 (7.15 g, 95%).

20
25

Synthesis of Allylic Alcohol 238 as illustrated in Figure 34. Methyl ester 237 (6.1 g, 14.4 mmol) was dissolved in THF (80 mL) and cooled to -78 °C. DIBAL (44.0

mL, 1 M solution in CH₂Cl₂, 44.0 mmol, 3.0 equiv) was added dropwise at -78 °C, and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with MeOH (1.0 mL) at -78 °C, and then ether (100 mL) was added, followed by saturated aqueous sodium-potassium tartrate solution (10 mL). The resulting mixture was allowed to warm up to room temperature, where it was stirred for 3 h. The organic layer was separated and the aqueous phase was extracted with ether (2 x 50 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 40 to 80% ether in hexanes) furnished alcohol 238 (5.58 g, 98%).

Synthesis of Compound 239 as illustrated in Figure 34.
Chlorination of Alcohol 238. Alcohol 238 (3.00 g, 7.60 mmol) was dissolved in CCl₄ (75 mL, 0.1 M) and Ph₃P (4.00 g, 15.2 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 10% ether in hexanes) furnished pure 239 (2.6 g, 83%).

Synthesis of Compound 240 as illustrated in Figure 34.
Reduction of 239. Compound 239 (2.60 g, 6.30 mmol) was dissolved in THF (60 mL, 0.1 M) and cooled to 0 °C. LiEt₃BH (12.6 mL, 1.0 M solution in THF, 12.6 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. Aqueous NaOH (1.0 mL, 3.0 N) solution was added followed by addition of Et₂O (150 mL). The organic phase was

washed with brine (2 x 20 mL), dried (MgSO₄) and concentrated. Flash column chromatography (silica gel, 20% ether in hexanes) furnished pure 240 (2.38 g, 99%).

5 **Synthesis of Primary Alcohol 241 as illustrated in Figure 34.** Selective Hydroboration of Olefinic Compound 240. Compound 240 (1.1 g, 2.91 mmol) was dissolved in THF (3.0 mL, 1.0 M) and the solution was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M solution in THF, 3.5 mmol, 1.2 equiv) was
10 added, and the reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH (7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with stirring, followed by H₂O₂ (2.4 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, after
15 which time the reaction mixture was diluted with ether (30 mL). The organic solution was separated and the aqueous phase was extracted with ether (2 x 15 mL). The combined organic layer was washed with brine (2 x 5 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silica gel, 50 & 80% ether in hexanes)
20 furnished primary alcohol 241 (1.0 g, 91%).

Synthesis of Iodide 242 as illustrated in Figure 34. Iodide 242 (1.18 g, 92%) was prepared from alcohol 241 (1.0 g, 2.53 mmol) according to the procedure described above for
25 219.

Synthesis of Hydrazone 243 as illustrated in Figure 34. Alkylation of SAMP Hydrazone with Iodide 242. SAMP hydrazone (337 mg, 0.2 mmol, 2.0 equiv) in THF (2.5 mL), was

added to a freshly prepared solution of LDA at 0 °C [diisopropylamine (277 mL, 0.20 mmol, 2.0 equiv) was added to n-BuLi (1.39 mL, 1.42 M solution in hexanes, 0.20 mmol, 2.0 equiv) in 2.5 mL of THF at 0 °C] at 0 °C. After stirring at
5 that temperature for 8 h, the resulting yellow solution was cooled to -100 °C, and a solution of iodide 242 (0.5 g, 0.99 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to -20 °C over 10 h, and then poured into saturated aqueous NH₄Cl
10 solution (5 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated. Purification by flash column chromatography on silica gel (20 & 40% ether in hexanes) provided hydrazone 243 (380 mg, 70%, de > 98% by ¹H NMR) as a yellow oil.

15 **Synthesis of Nitrile 244 as illustrated in Figure 35.** Monoperoxyphthalic acid magnesium salt (MMPP·6H₂O, 233 mg, 0.38 mmol, 2.5 equiv) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 3.0 mL) at 0
20 °C. Hydrazone 243 (83 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the mixture was stirred at 0 °C until the reaction was complete by TLC (ca 1 h). The resulting suspension was placed in a separating funnel along with ether (15 mL) and saturated aqueous NaHCO₃ solution (5
25 mL). The organic layer was separated and the aqueous phase was extracted with ether (10 mL). The combined organic solution was washed with water (5 mL) and brine (5 mL), dried (MgSO₄) and concentrated. Flash column chromatography

(silica gel, 50% ether in hexanes) afforded nitrile 244 (53 mg, 80%) as a colorless oil.

Synthesis of Aldehyde 224 as illustrated in Figure 35.

5 Nitrile 244 (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to -78 °C. DIBAL (245 mL, 1 M solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca 1 h). Methanol
10 (150 mL) and aqueous HCl (150 mL, 1 N solution) were sequentially added and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 x 5
15 mL) and the combined organic solution was washed with brine (5 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 15% ether in hexanes) furnished pure aldehyde 224 (44 mg, 82%):

20 **Synthesis of tris(Silylether) 245 as illustrated in Figure 35.** Aldol Reaction of Ketone with Aldehyde 224. A solution of ketone (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise to a freshly prepared solution of LDA (diisopropylamine (94 mL, 0.67 mmol) was added to n-BuLi (0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of
25 THF at 0 °C) in THF (2.5 mL) at -78 °C. After stirring for 15 min at -78 °C, the solution was allowed to warm to -40 °C over a period of 1 h. The reaction mixture was cooled to -78 °C, and a solution of aldehyde 224 (244 mg, 0.56 mmol, 1.0

equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at -78 °C, and then quenched by dropwise addition of saturated aqueous NH₄Cl solution (2 mL). The aqueous phase was extracted with ether (3 x 5 mL) and the combined organic layer was dried (MgSO₄) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products (354 mg (85%) of ca 3:1 by ¹H NMR). Separation of these diastereoisomers was carried out by preparative thin layer chromatography (silica gel, 20% ether in hexanes) leading to pure 245 (270 mg, 64%).

Synthesis of tetra(Silylether) 246 as illustrated in Figure 35. Compound 245 (275 mg, 0.33 mmol) was dissolved in CH₂Cl₂ (5.0 mL), cooled to 0 °C and treated with 2,6-lutidine (76 mL, 0.66 mmol, 2.0 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (88 mL, 0.39 mmol, 1.2 equiv). After stirring for 2 h at 0 °C, the reaction mixture was quenched with aqueous HCl (5 mL, 1.0 N solution) and the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic solution was washed with brine (5 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetra(silylether) 246 (300 mg, 96%) as a colorless oil.

Synthesis of Alcohol 247 as illustrated in Figure 35. Alcohol 247 (200 mg, 85%) was obtained from compound 246 (264

mg, 0.28 mmol) according to the procedure described above for 223.

Synthesis of Aldehyde 248 as illustrated in Figure 35.

5 Oxidation of Alcohol 247. To a solution of oxalyl chloride (54 mL, 0.61 mmol, 2.0 equiv) in CH₂Cl₂ (5.0 mL) was added dropwise DMSO (86 mL, 1.21 mmol, 4.0 equiv) at -78 °C. After stirring for 15 min at -78 °C, a solution of alcohol 247 (255 mg, 0.305 mmol, 1.0 equiv) in CH₂Cl₂ (2.0 mL) was added
10 dropwise at -78 °C over a period of 5 min. The solution was stirred at -78 °C for 30 min, and then Et₃N (250 mL, 1.82 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to 0 °C over a period of 30 min and then ether (20 mL) was added, followed by saturated aqueous NH₄Cl solution
15 (10 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 x 10 mL). The combined organic solution was dried (MgSO₄), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided
20 aldehyde 248 (241 mg, 95%) as a colorless oil.

Synthesis of Carboxylic Acid 249 as illustrated in Figure 35. Aldehyde 248 (224 mg, 0.29 mmol), tBuOH (5.0 mL), isobutylene (5.0 mL, 2 M solution in THF, 10.0 mmol),
25 H₂O (1.0 mL), NaClO₂ (90 mg, 0.86 mmol, 3.0 equiv) and NaH₂PO₄ (60 mg, 0.43 mmol, 1.5 equiv) were combined and stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was

subjected to flash column chromatography (silica gel, 6% MeOH in CH₂Cl₂) to afford carboxylic acid 249 (220 mg, 90%).

Synthesis of Hydroxy Acid 250 as illustrated in Figure

5 35. A solution of tris(silyl) ether 249 (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous
10 solution was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (10 mL), dried (MgSO₄) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH₂Cl₂) to provide hydroxy acid 250 (203 mg, 78%) as a yellow oil:

15

Synthesis of Lactone 229 as illustrated in Figure 36.

Macrolactonization of Hydroxy Acid 250. A solution of hydroxy acid 250 (140 mg, mixture of Z and E isomers, ca 1:1, 0.189 mmol) in THF (2.6 mL) was treated at 0 °C with Et₃N (58
20 mL, 0.416 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (29.4 mL, 0.246 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added to a solution of 4-DMAP (233 mg, 1.896 mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 °C and stirred at that
25 temperature for 10 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by preparative thin layer chromatography (silica gel, 5% MeOH in CH₂Cl₂), gave pure lactone 229 (104 mg, 77%).

Synthesis of Compound 252 as illustrated in Figure 37. Compound 251, trityl chloride (2.0 eq.) and DMAP (1.1 eq.) were dissolved in DMF (0.1 M) and the reaction mixture heated at 60 °C for 12 h. The solvent was removed under reduced pressure and flash column chromatography (silica gel, ether in hexanes) furnished pure 252.

Synthesis of Primary Alcohol 253 as illustrated in Figure 37. Selective Hydroboration of Olefinic Compound 252. Compound 252 was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M solution in THF, 3.5 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH (7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with stirring, followed by H₂O₂ (2.4 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, after which time the reaction mixture was diluted with ether (30 mL). The organic solution was separated and the aqueous phase was extracted with ether (2 x 15 mL). The combined organic layer was washed with brine (2 x 5 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silica gel, 50 to 80% ether in hexanes) furnished primary alcohol 254 (1.0 g, 91%).

Synthesis of Iodide 254 as illustrated in Figure 37. Iodide 254 (1.18 g, 92%) was prepared from alcohol 253 (1.0 g, 2.53 mmol) according to the procedure described above for 219.

Synthesis of Hydrazone 255 as illustrated in Figure 37. Alkylation of SAMP Hydrazone with Iodide 254. SAMP hydrazone (337 mg, 0.2 mmol, 2.0 equiv) in THF (2.5 mL), was added to a freshly prepared solution of LDA at 0 °C [diisopropylamine (277 mL, 0.20 mmol, 2.0 equiv) was added to n-BuLi (1.39 mL, 1.42 M solution in hexanes, 0.20 mmol, 2.0 equiv) in 2.5 mL of THF at 0 °C] at 0 °C. After stirring at that temperature for 8 h, the resulting yellow solution was cooled to -100 °C, and a solution of iodide 254 (0.5 g, 0.99 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to -20 °C over 10 h, and then poured into saturated aqueous NH₄Cl solution (5 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated. Purification by flash column chromatography on silica gel (20 to 40% ether in hexanes) provided hydrazone 255 (380 mg, 70%, de > 98% by ¹H NMR) as a yellow oil.

Synthesis of Nitrile 256 as illustrated in Figure 37. Monoperoxyphthalic acid magnesium salt (MMPP·6H₂O, 233 mg, 0.38 mmol, 2.5 equiv) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 3.0 mL) at 0 °C. Hydrazone 255 (83 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the mixture was stirred at 0 °C until the reaction was complete by TLC (ca 1 h). The resulting suspension was placed in a separating funnel along with ether (15 mL) and saturated aqueous NaHCO₃ solution (5 mL). The organic layer was separated and the aqueous phase was extracted with ether (10 mL). The combined organic

solution was washed with water (5 mL) and brine (5 mL), dried (MgSO₄) and concentrated. Flash column chromatography (silica gel, 50% ether in hexanes) afforded nitrile 256 (53 mg, 80%) as a colorless oil.

5

Synthesis of Aldehyde 257 as illustrated in Figure 37. Nitrile 256 (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to -78 °C. DIBAL (245 mL, 1 M solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca 1 h). Methanol (150 mL) and aqueous HCl (150 mL, 1 N solution) were sequentially added and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 x 5 mL) and the combined organic solution was washed with brine (5 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 15% ether in hexanes) furnished pure aldehyde 257 (44 mg, 82%).

10

15

20

Synthesis of tris(Silylether) 258 as illustrated in Figure 38. Aldol Reaction of Ketone with Aldehyde 257. A solution of ketone (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (94 mL, 0.67 mmol) was added to n-BuLi (0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of THF at 0 °C] in THF (2.5 mL) at -78 °C. After stirring for

25

15 min at -78 °C, the solution was allowed to warm to -40 °C over a period of 1 h. The reaction mixture was cooled to -78 °C, and a solution of aldehyde 257 (244 mg, 0.56 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at -78 °C, and then quenched by dropwise addition of saturated aqueous NH₄Cl solution (2 mL). The aqueous phase was extracted with ether (3 x 5 mL) and the combined organic layer was dried (MgSO₄) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products (354 mg (85%) of ca 3:1 by ¹H NMR). Separation of these diastereoisomers was carried out by preparative thin layer chromatography (silica gel, 20% ether in hexanes) leading to pure 258 (270 mg, 64%).

Synthesis of tetra(Silylether) 259 as illustrated in Figure 38. Compound 258 (275 mg, 0.33 mmol) was dissolved in CH₂Cl₂ (5.0 mL), cooled to 0 °C and treated with 2,6-lutidine (76 mL, 0.66 mmol, 2.0 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (88 mL, 0.39 mmol, 1.2 equiv). After stirring for 2 h at 0 °C, the reaction mixture was quenched with aqueous HCl (5 mL, 1.0 N solution) and the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic solution was washed with brine (5 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetra(silylether) 259 (300 mg, 96%) as a colorless oil.

Synthesis of Alcohol 260 as illustrated in Figure 38. Alcohol 260 (200 mg, 85%) was obtained from compound 259 (264 mg, 0.28 mmol) according to the procedure described above for 223.

5

Synthesis of Aldehyde 261 as illustrated in Figure 38.

Oxidation of Alcohol 260. To a solution of oxalyl chloride (54 mL, 0.61 mmol, 2.0 equiv) in CH₂Cl₂ (5.0 mL) was added dropwise DMSO (86 mL, 1.21 mmol, 4.0 equiv) at -78 °C. After stirring for 15 min at -78 °C, a solution of alcohol 260 (255 mg, 0.305 mmol, 1.0 equiv) in CH₂Cl₂ (2.0 mL) was added dropwise at -78 °C over a period of 5 min. The solution was stirred at -78 °C for 30 min, and then Et₃N (250 mL, 1.82 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to 0 °C over a period of 30 min and then ether (20 mL) was added, followed by saturated aqueous NH₄Cl solution (10 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 x 10 mL). The combined organic solution was dried (MgSO₄), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde 261 (241 mg, 95%) as a colorless oil.

25

Synthesis of Carboxylic Acid 262 as illustrated in Figure 38. Oxidation of Aldehyde 261. Aldehyde 261 (224 mg, 0.29 mmol), tBuOH (5.0 mL), isobutylene (5.0 mL, 2 M solution in THF, 10.0 mmol), H₂O (1.0 mL), NaClO₂ (90 mg, 0.86 mmol, 3.0 equiv) and NaH₂PO₄ (60 mg, 0.43 mmol, 1.5 equiv) were combined and stirred at room temperature for 1 h.

The reaction mixture was concentrated under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 6% MeOH in CH₂Cl₂) to afford carboxylic acid 262 (220 mg, 90%).

5

Synthesis of Hydroxy Acid 263 as illustrated in Figure 38. Selective Desilylation of 262. A solution of tris(silyl) ether 262 (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (10 mL), dried (MgSO₄) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH₂Cl₂) to provide hydroxy acid 263 (203 mg, 78%) as a yellow oil.

10

15

Synthesis of Lactone 264 as illustrated in Figure 38. Macrolactonization of Hydroxy Acid 263. A solution of hydroxy acid 263 (1.0 eq) in THF (0.07 M) was treated at 0 °C with Et₃N (2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added to a solution of 4-DMAP (2.0 equiv) in toluene (0.002 M) at 25 °C and stirred at that temperature for 6 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by

20

25

preparative thin layer chromatography (silica gel, 5% MeOH in CH₂Cl₂), gave pure lactone 264 (77%).

Synthesis of Triol 265 as illustrated in Figure 39.

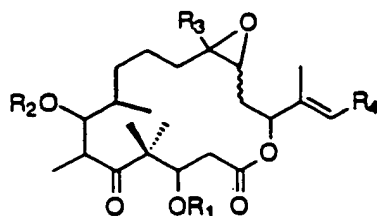
5 HF.pyr (0.25%) was carefully added to a solution of 264 (1.0 eq.) in THF (0.05 M) and the reaction mixture stirred for 24 hours at 25 °C. Aqueous saturated NaHCO₃ solution was added followed by extraction with ethyl acetate. The organic phase was dried (MgSO₄) and concentrated. The crude mixture was
10 purified by flash column chromatography (silica gel, 5% MeOH in CH₂Cl₂) to provide triol 265 (78%).

Synthesis of Epoxyde 266 as illustrated in Figure 39.

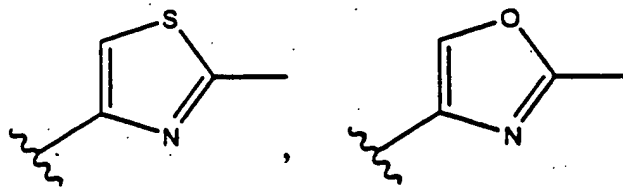
15 The epoxidation of 265 according to the procedure described above for 232 led to epothilone 266.

What is claimed:

1. A method for synthesizing an epothilone analog represented by the following structure:

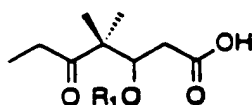


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:

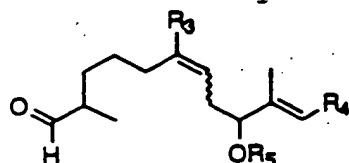


which comprises the following steps:

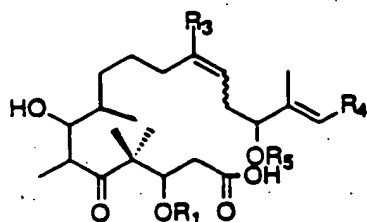
Step A: condensing a keto acid represented by the following structure:



with an aldehyde represented by the following structure:

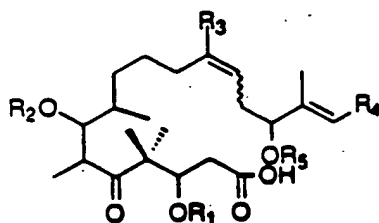


wherein R_5 is selected from the group consisting of tert-butyltrimethylsilyl and trimethylsilyl, for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:



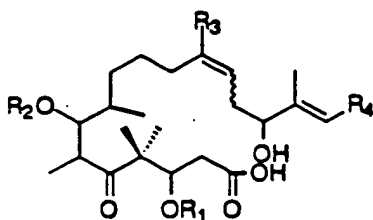
; then

Step B: derivatizing the free hydroxyl moiety of said carboxylic acid of Step A with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyltrimethylsilyl chloride, tert-butyltrimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:



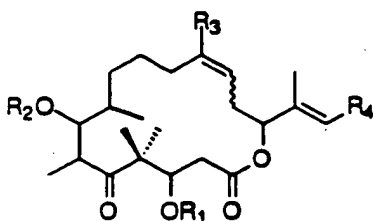
; then

Step C: regioselectively deprotecting the R_5 protected hydroxyl moiety of the derivatized carboxylic acid of said step B for producing a hydroxy acid with the following structure:



; then

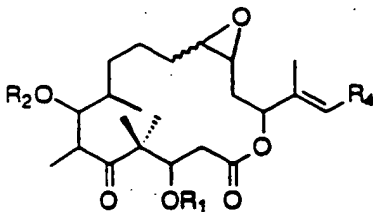
Step D: macrolactonizing the hydroxy acid of said Step C for producing a macrolide with the following structure:



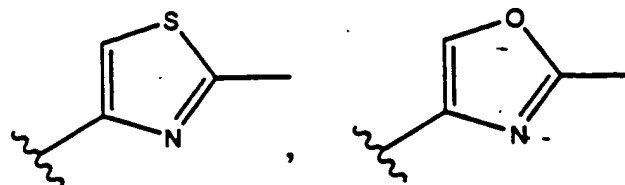
; and then

Step E: epoxidizing the macrolide of said Step D for producing the epothilone analog.

2. A method for synthesizing an epothilone analog represented by the following structure:

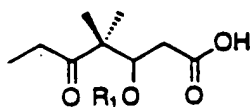


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:

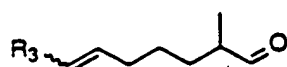


which comprises:

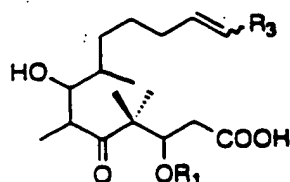
Step A: condensing a keto acid represented by the following structure:



with an aldehyde represented by the following structure:

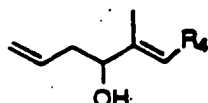


wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$ - (solid phase support), for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:

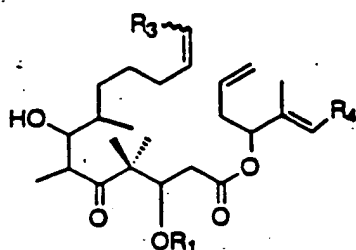


; then

Step B: esterifying the carboxylic acid of said Step A with a secondary alcohol represented by the following structure:

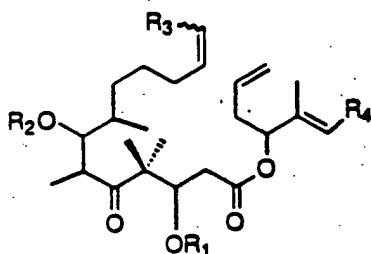


for producing an ester with a free hydroxyl moiety represented by the following structure:



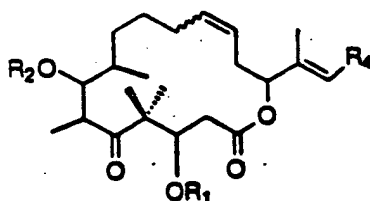
; then

Step C: derivatizing the free hydroxyl moiety of said ester of Step B with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxymino)-2-phenylacetonitrile for producing a derivatized ester represented by the following structure:



; then

Step D: metathesizing the derivatized ester of said Step C with an organo-metallic catalyst for producing a macrolide with the following structure:



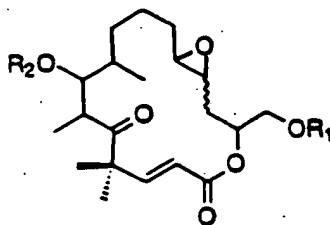
; and then

Step E: epoxidizing the macrolide of said Step D for producing the epothilone analog.

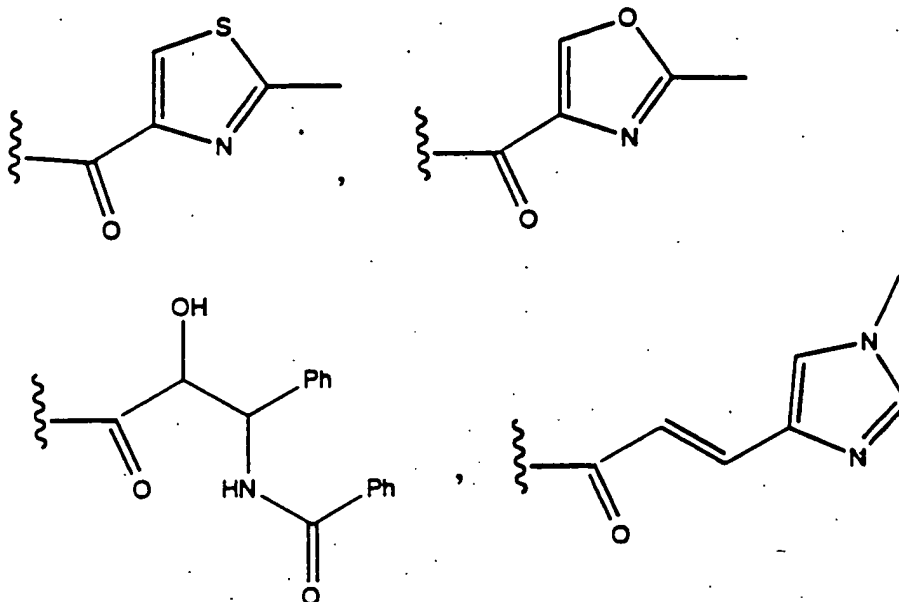
3. The method as described in Claim 2 wherein the organo-metallic catalyst is selected from the group consisting of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

4. The method as described in Claim 3 wherein the solid support is selected from the group consisting of Merrifield resin, PEG-polystyrene, hydroxymethyl polystyrene, formyl polystyrene, aminomethyl polystyrene and phenolic polystyrene.

5. A method for synthesizing an epothilone analog represented by the following structure:

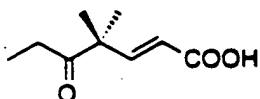


wherein R₁ is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:

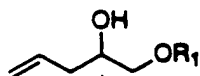


wherein R_2 is selected from the group consisting of, hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; which comprises the following steps:

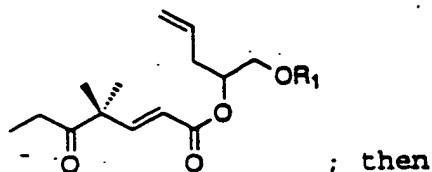
Step A: esterifying a keto acid represented by the following structure:



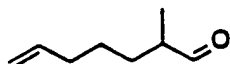
with an alcohol represented by the following structure:



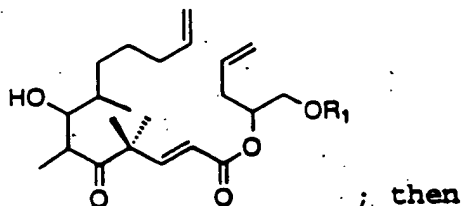
for producing an ester represented by the following structure:



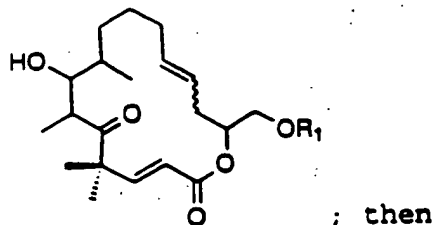
Step B: condensing the ester of said Step A with an aldehyde represented by the following structure:



for producing a bis-terminal olefin with the following structure:

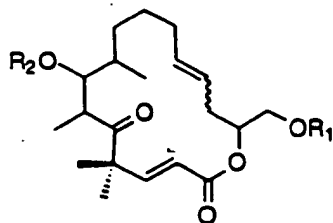


Step C: metathesizing the bis-terminal olefin of said Step B with an organo-metallic catalyst for producing a macrocyclic lactone with a free hydroxyl moiety represented by the following structure:



Step D: derivatizing the free hydroxyl of the macrocyclic lactone of Step C with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of hydrogen, tert-butyltrimethylsilyl chloride, tert-butyltrimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl

chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized macrolide with the following structure:

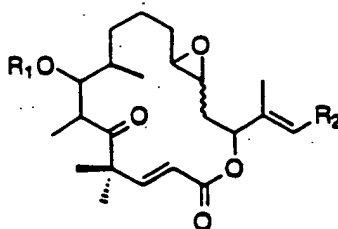


; and then

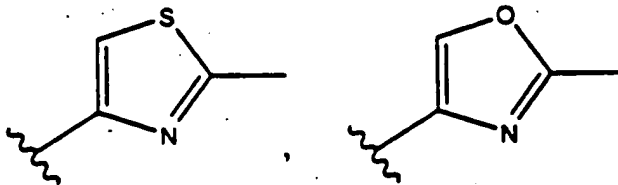
Step E: epoxidizing the derivatized macrolide of said Step D for producing the epothilone analog.

6. The method as described in Claim 5 wherein the organo-metallic catalyst is selected from the group consisting of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

7. A method for synthesizing an epothilone analog represented by the following structure:

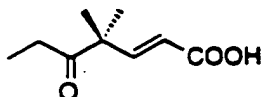


wherein R₁ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R₂ is selected from the group represented by the following structures:

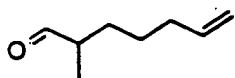


which comprises the following steps:

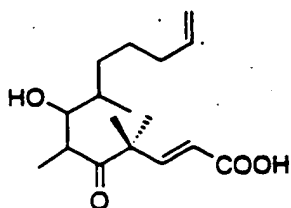
Step A: condensing a keto acid represented by the following structure:



with an aldehyde represented by the following structure:

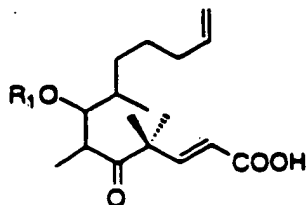


for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:



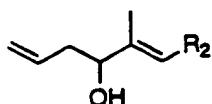
; then

Step B: derivatizing the free hydroxyl moiety of said carboxylic acid of Step A with a derivatizing agent represented by the formula R_1-X wherein R_1-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:

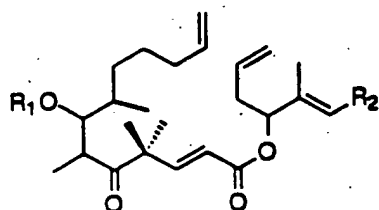


; then

Step C: esterifying the derivatized carboxylic acid of said Step B with an alcohol 1 represented by the following structure:

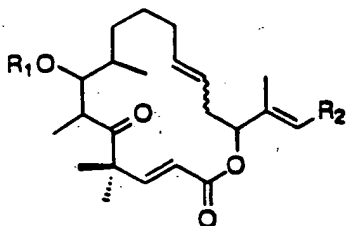


for producing a bis-terminal olefin with the following structure:



; and then

Step D: metathesizing the bis-terminal olefin of said Step C with an organo-metallic catalyst for producing a macrocyclic lactone with the following structure:

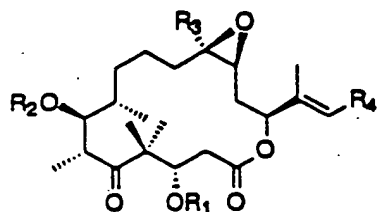


; then

Step E: epoxidizing the macrocyclic lactone of Step D producing the epothilone analog.

8. The method as described in Claim 7 wherein the organo-metallic catalyst is selected from the group consisting of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

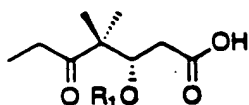
9. A method for synthesizing an epothilone analog represented by the following structure:



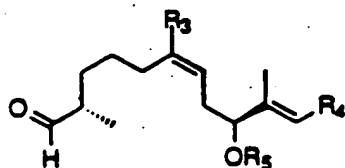
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:



which comprises the following steps:
Step A: condensing a keto acid represented by the following structure:

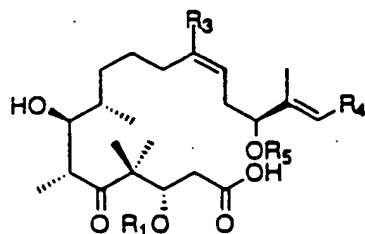


with an aldehyde represented by the following structure:



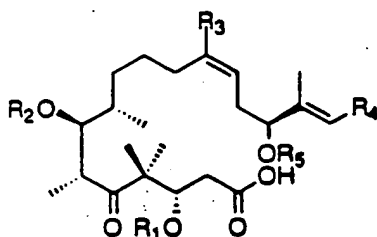
wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl, for producing a

carboxylic acid with a free hydroxyl moiety represented by the following structure:



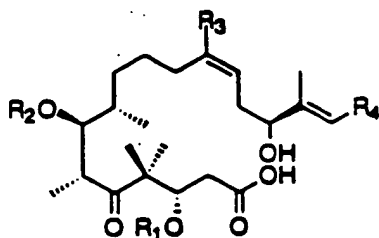
; then

Step B: derivatizing the free hydroxyl moiety of said carboxylic acid of Step A with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxymino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:



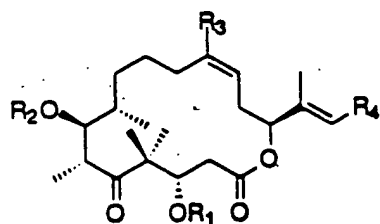
; then

Step C: regioselectively deprotecting the R_5 protected hydroxyl moiety of the derivatized carboxylic acid of said step B for producing a hydroxy acid with the following structure:



; then

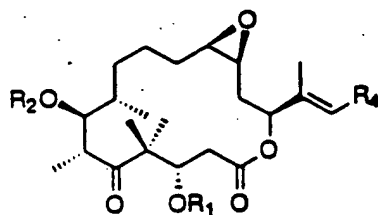
Step D: macrolactonizing the hydroxy acid of said Step C for producing a macrolide having a Z-olefin with the following structure:



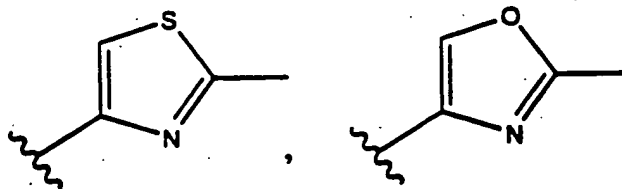
; and then

Step E: epoxidizing the macrolide of said Step D for producing the epothilone analog.

10. A method for synthesizing an epothilone analog represented by the following structure:



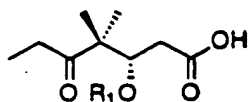
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:



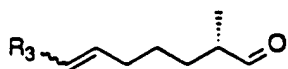
which comprises:

Step A: condensing a keto acid represented by the

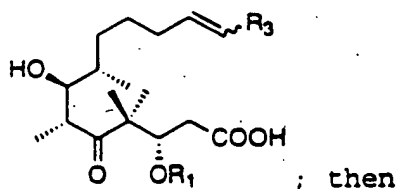
following structure:



5 with an aldehyde represented by the following structure:

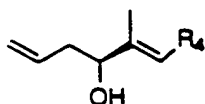


10 wherein R_3 is selected from the group consisting of H and $(CH_2)_n$ - (solid phase support) wherein $1 \leq n \leq 20$, for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:



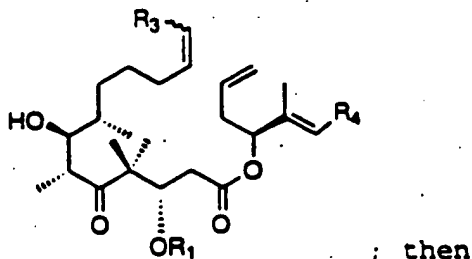
15

Step B: esterifying the carboxylic acid of said Step A with a secondary alcohol represented by the following structure:



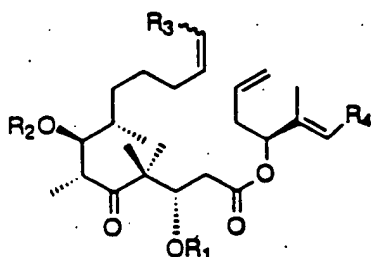
20

for producing an ester with a free hydroxyl moiety represented by the following structure:



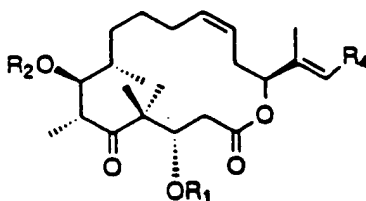
25

Step C: derivatizing the free hydroxyl moiety of said ester of Step B with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized ester represented by the following structure:



; then

Step D: Metathesizing the derivatized ester of said Step C with an organo-metallic catalyst for producing a macrolide with the following structure:



; and then

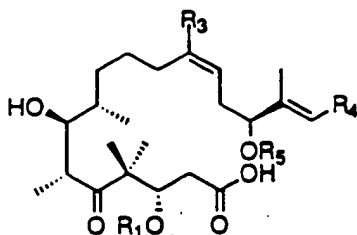
Step E: epoxidizing the macrolide of said Step D for producing the epothilone analog.

11. The method as described in Claim 10 wherein the organo-metallic catalyst is selected from the group consisting of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

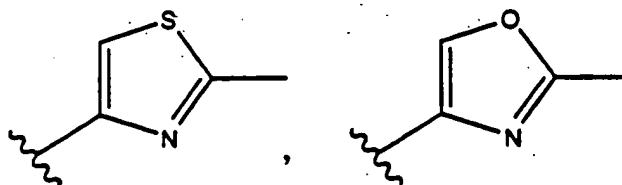
12. The method as described in Claim 10 wherein the solid support is selected from the group consisting of Merrifield resin, PEG-polystyrene, hydroxymethyl

polystyrene, formyl polystyrene, aminomethyl polystyrene and phenolic polystyrene.

- 5 13. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:

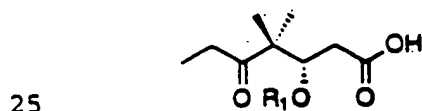


- 10 wherein R₁ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R₃ is selected from the group consisting of hydrogen, methyl, -CH₂OH, -CH₂Cl, and -CH₂CO₂H; wherein R₄ is selected from the group represented by the formula:
- 15

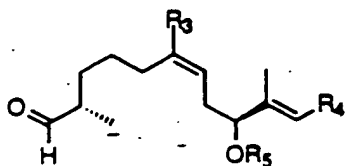


- 20 wherein R₅ is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl;

which comprises the step of condensing a keto acid represented by the following structure:

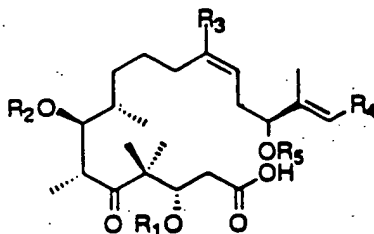


with an aldehyde represented by the following structure:



for producing the advanced intermediate.

- 5 14. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:

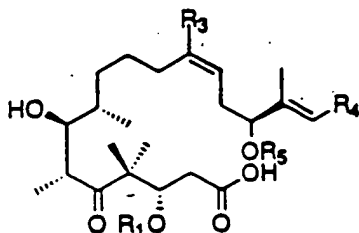


- 10 wherein R_1 is selected from the group consisting of, hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:

20

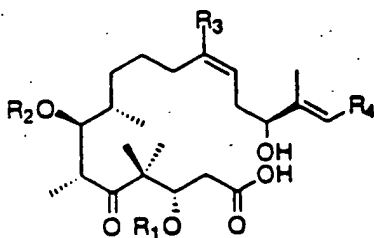


- 25 wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl; which comprises the step of derivatizing the free hydroxyl moiety of a carboxylic acid represented by the following structure:

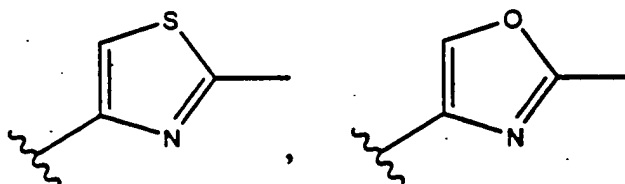


with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxy-carbonyl-oxyimino)-2-phenylacetone nitrile for producing the advanced intermediate.

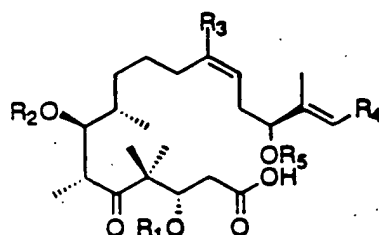
15. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

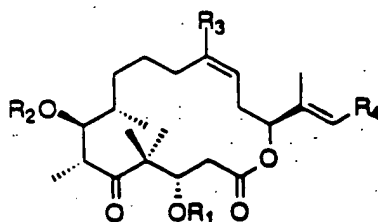


which comprises the step of regioselectively deprotecting a R_5 protected hydroxyl moiety of a derivatized carboxylic acid represented by the following structure:

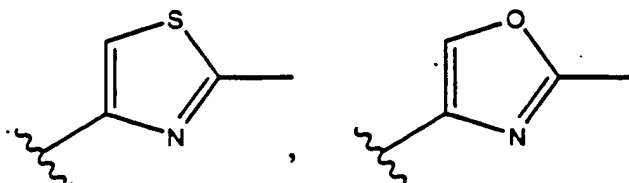


wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl, for producing the advanced intermediate.

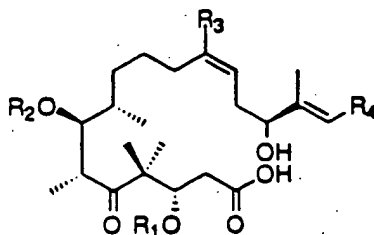
16. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:

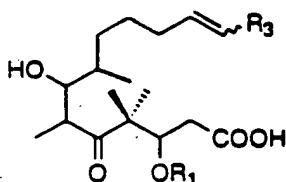


5 which comprises the step of macrolactonizing a hydroxy acid represented by the following structure:



10 for producing the advanced intermediate.

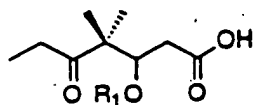
17. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:



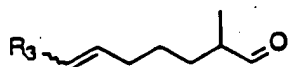
15 wherein R_1 is selected from the group consisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$ - (solid phase support);

20 which comprises:

25 Step A: condensing a keto acid represented by the following structure:

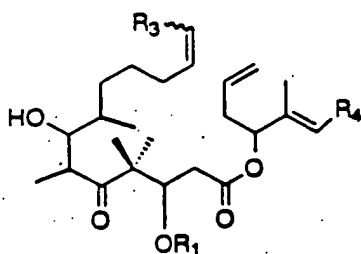


with an aldehyde represented by the following structure:

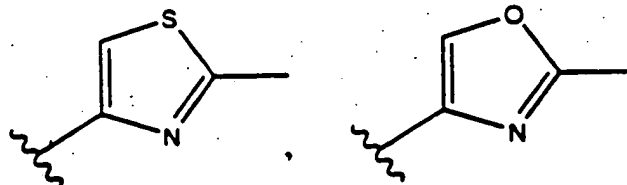


for producing the advanced intermediate.

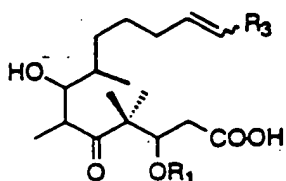
18. A method for synthesizing an advanced intermediate of an epothilone analog represented by the following structure:



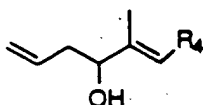
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$ - (solid phase support); wherein R_4 is selected from the group represented by the formulas:



which comprises the step of esterifying a carboxylic acid with a free hydroxyl moiety represented by the following structure:

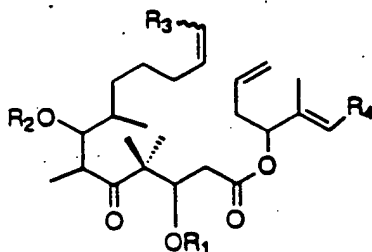


with a secondary alcohol represented by the following structure:

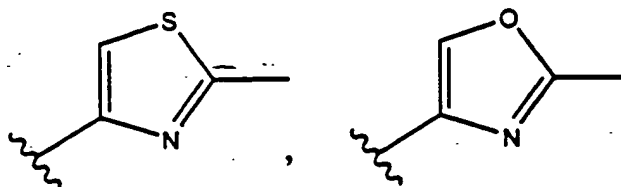


for producing the advanced intermediate.

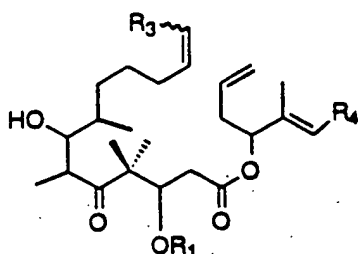
19. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$ - (solid phase support); wherein R_4 is selected from the group represented by the formulas:

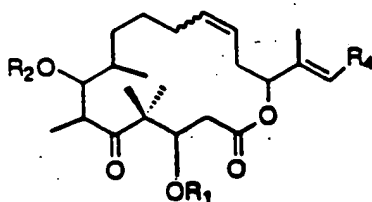


which comprises the step of derivatizing the free hydroxyl moiety of an ester represented by the following structure:



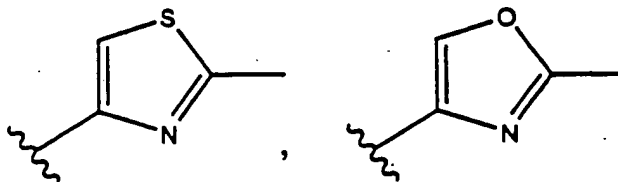
with a derivatizing agent represented by the formula R₂-X wherein R₂-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing the advanced intermediate.

20. A method for synthesizing an advanced intermediate of an epothilone analog represented by the following structure:

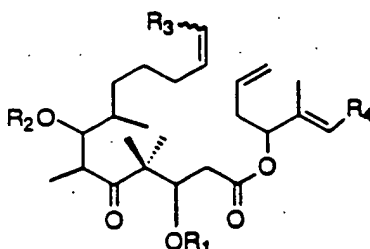


wherein R₁ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R₂ is selected from the group consisting of hydrogen, tert-

butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:

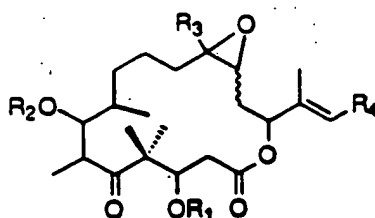


which comprises the step of metathesizing a derivatized ester represented by the following structure:



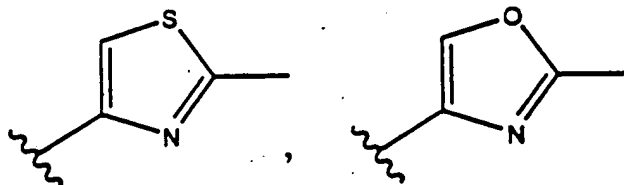
wherein R_3 is selected from the group consisting of $(CH_2)_n$ -(solid phase support); with an organo-metallic catalyst selected from the group consisting of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-*t*-butoxide) for producing the advanced intermediate.

21. A method for synthesizing an epothilone analog represented by the following structure:

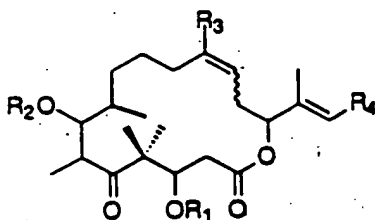


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is

selected from the group consisting of hydrogen, tert-butyl dimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:

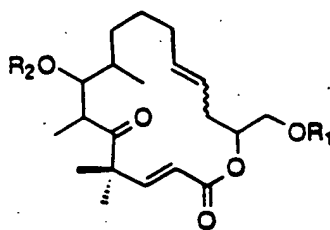


which comprises the step of regioselectively epoxidizing a macrolide with the following structure:

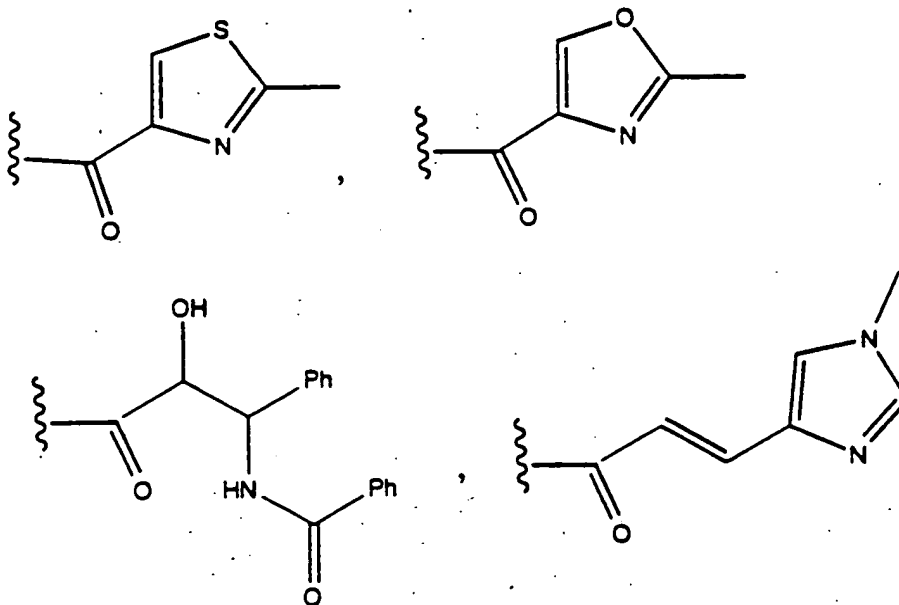


for producing the epothilone analog.

22. A method for synthesizing an advanced intermediate of an epothilone analog represented by the following structure:

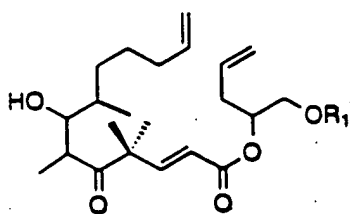


wherein R_1 is selected from the group consisting of hydrogen, tert-butyl diphenylsilyl, tert-butyl dimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formula:



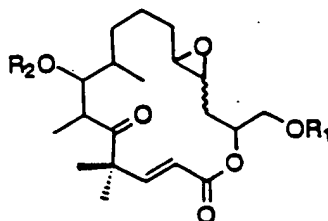
wherein R_2 is selected from the group consisting of
 5 hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
 acetyl, benzoyl, and tert-butoxycarbonyl;

which comprises the step of metathesizing a bis-terminal
 10 olefin of represented by the following structure:

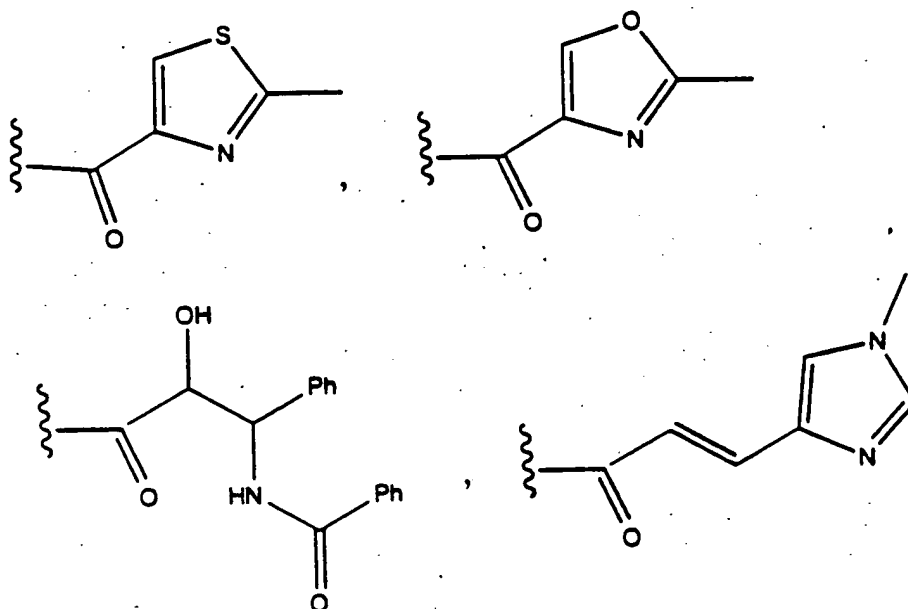


with an organo-metallic catalyst selected from the group
 15 consisting of bis(tricyclohexylphosphine)benzylidene
 ruthenium dichloride, and 2,6-diisopropylphenylimido
 neophylidenemolybdenum bis(hexafluoro-t-butoxide) for
 producing the advanced intermediate.

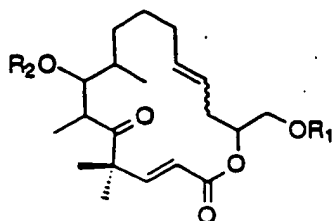
23. A method for synthesizing an epothilone analog
 20 represented by the following structure:



5 wherein R₁ is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formula:

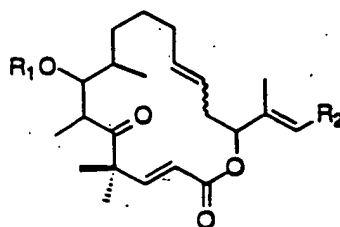


10 wherein R₂ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl;
 15 which comprises the step of epoxidizing a derivatized macrolide represented by the following structure:

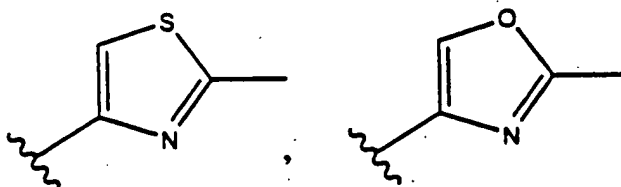


for producing the epothilone analog.

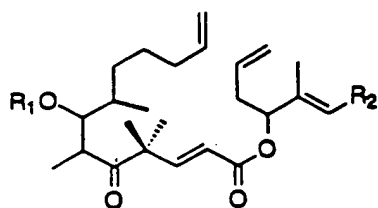
- 5 24. A method for synthesizing an advanced intermediate of an epothilone analog represented by the following structure:



- 10 wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein ;
 15 wherein R_2 is selected from the group represented by the following structures:

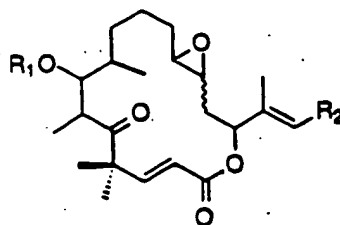


- 20 which comprises the step of metathesizing a bis-terminal olefin represented by the following structure:

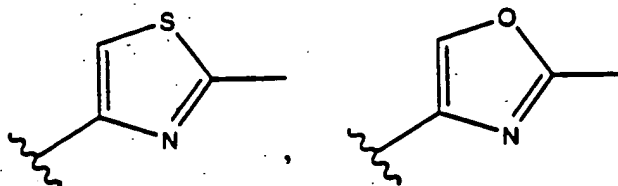


with an organo-metallic catalyst selected from the group consisting of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide) for producing the advanced intermediate.

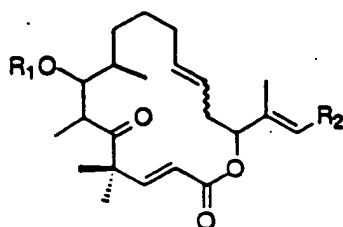
25. A method for synthesizing an epothilone analog represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group represented by the following structures:

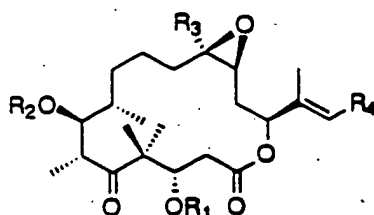


which comprises the step of epoxidizing a macrocyclic lactone represented by the following structure:



for producing the epothilone analog.

- 5 26. An epothilone analog represented by the following structure:

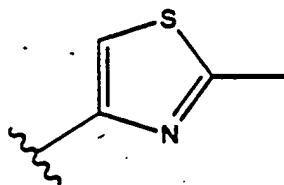


- 10 wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is
 15 selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:



- 20 with the proviso that if R_3 is selected from the group consisting of methyl and hydrogen and R_4 is selected from the group represented by the formula:

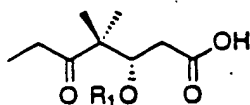
25



than R_1 and R_2 cannot be simultaneously hydrogen.

5

27. An epothilone analog intermediate represented by the following structure:

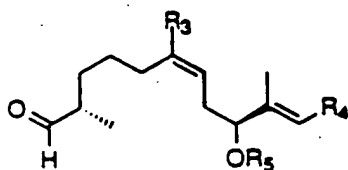


10

wherein R_1 is selected from the group consisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl.

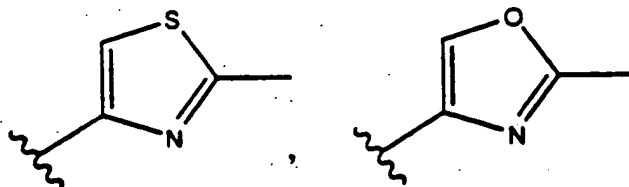
15

28. An epothilone analog intermediate represented by the following structure:



20

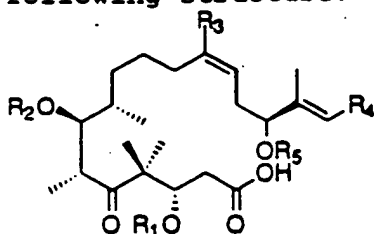
wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formula:



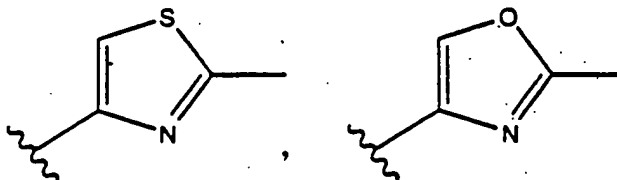
25

and wherein R_5 is selected from the group consisting of *tert*-butyldimethylsilyl and trimethylsilyl.

29. An epothilone analog intermediate represented by the following structure:



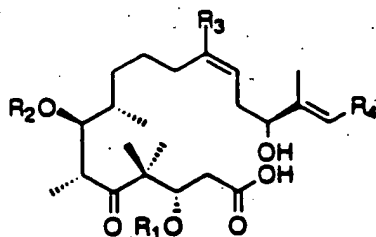
- 5 wherein R_1 is selected from the group consisting of hydrogen, tert-butyl dimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyl dimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formula:



15

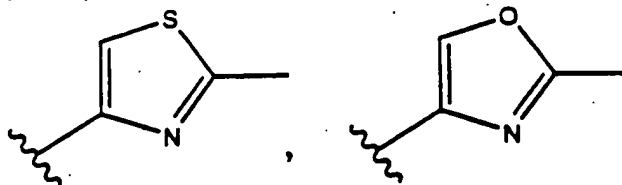
and wherein R_5 is selected from the group consisting of hydrogen, tert-butyl dimethylsilyl and trimethylsilyl.

- 20 30. An epothilone analog intermediate represented by the following structure:

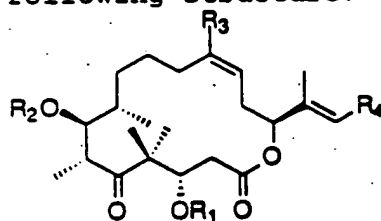


- 25 wherein R_1 is selected from the group consisting of hydrogen, tert-butyl dimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyl dimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formula:

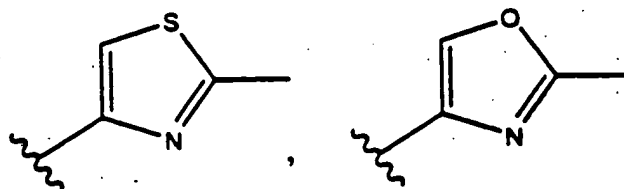
acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:



31. An epothilone analog intermediate represented by the following structure:

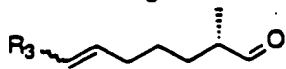


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:



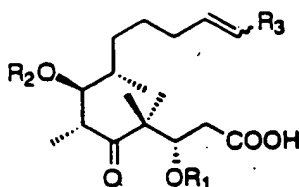
32. An epothilone analog intermediate represented by the

following structure:



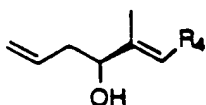
wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$ - (solid phase support).

33. An epothilone analog intermediate represented by the following structure:

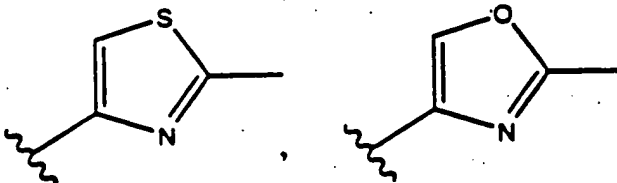


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl and wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$ - (solid phase support).

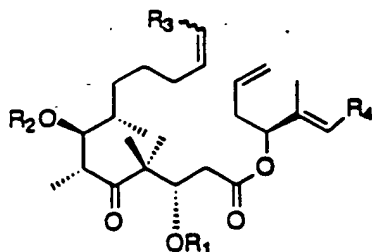
34. An epothilone analog intermediate represented by the following structure:



wherein R_4 is selected from the group represented by the formulas:



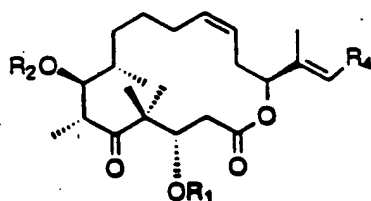
35. An epothilone analog intermediate represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

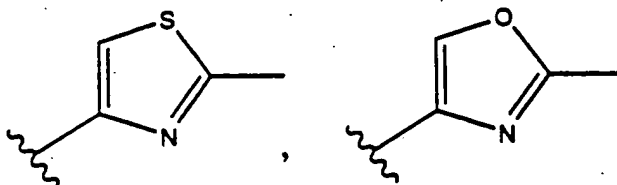


36. An epothilone analog intermediate represented by the following structure:

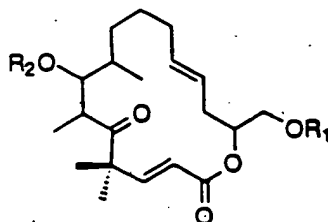


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is

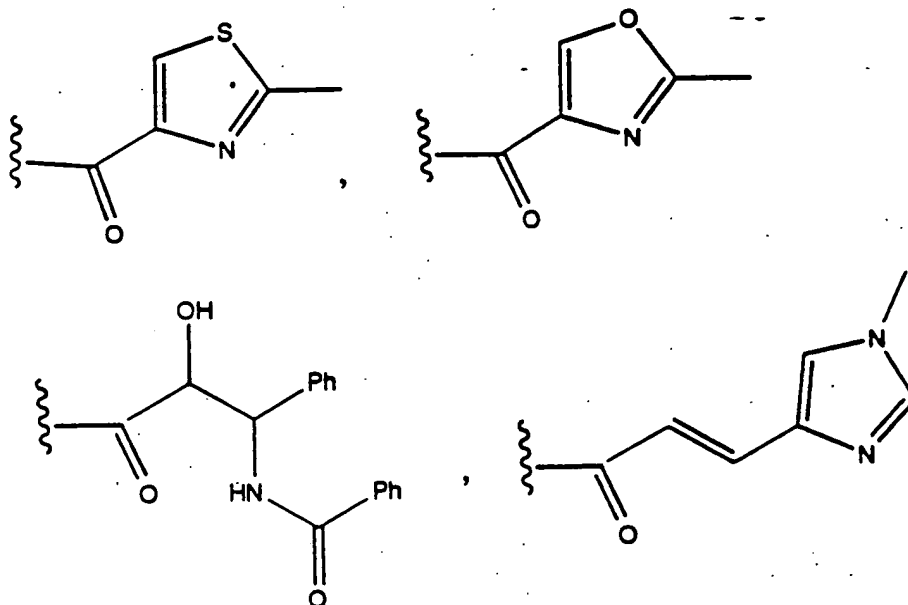
selected from the group consisting of hydrogen, tert-butyl-
dimethylsilyl, trimethylsilyl, methyl, acetyl,
benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected
from the group represented by the formulas:



37. An epothilone analog represented by the
following structure:

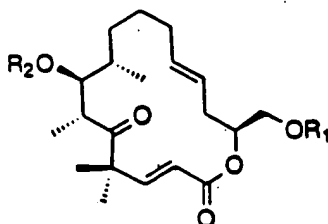


wherein R_1 is selected from the group consisting of
hydrogen, tert-butyl-diphenylsilyl, tert-
butyldimethylsilyl, trimethylsilyl, methyl, acetyl,
benzoyl, tert-butoxycarbonyl and the group represented by
the formulas:

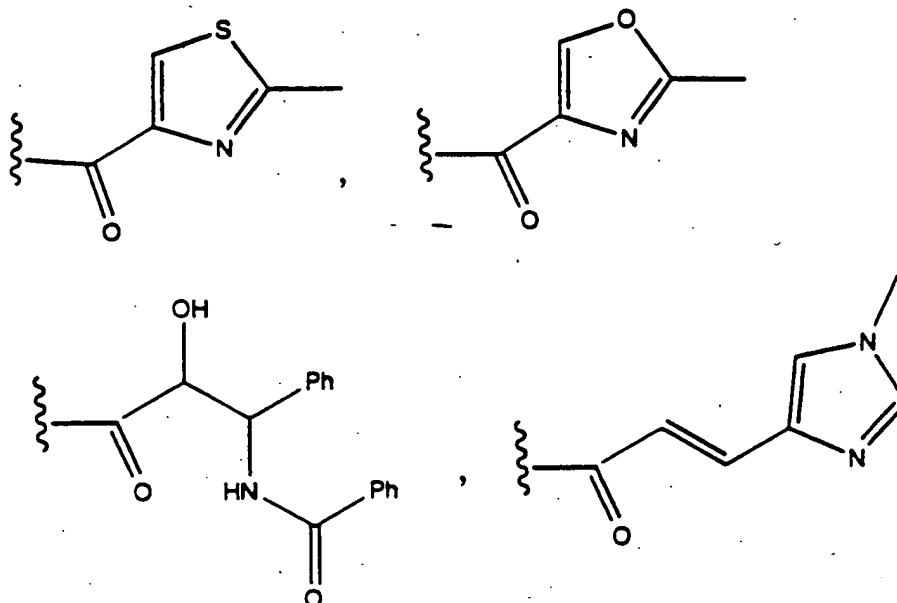


wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

38. An epothilone analog represented by the following structure:



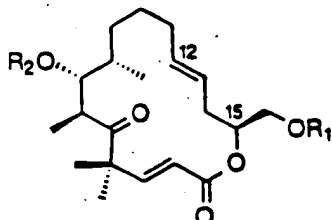
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:



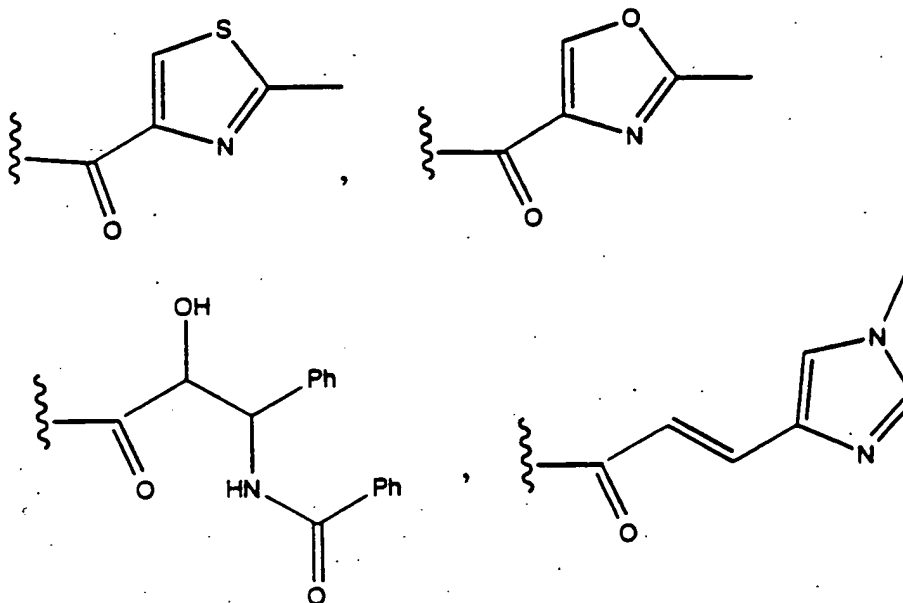
wherein R₂ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

5

39. An epothilone analog represented by the following structure:

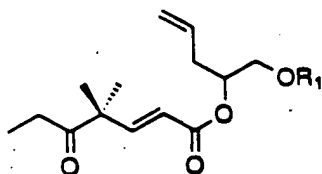


wherein R₁ is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formula:

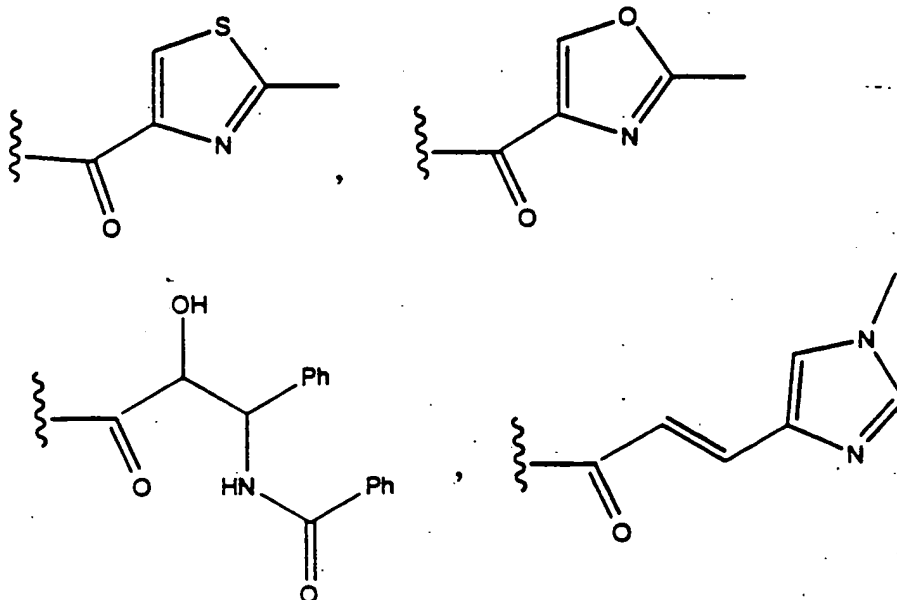


wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

40. An epothilone analog intermediate represented by the following structure:

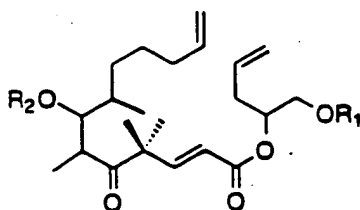


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:



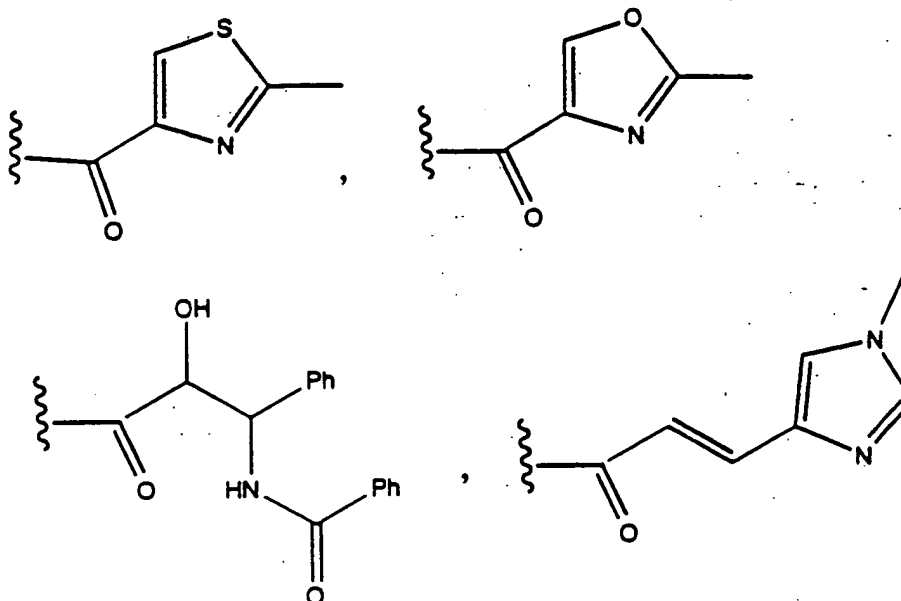
5 wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

41. An epothilone analog intermediate represented by the following structure:



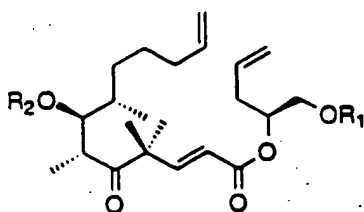
10

15 wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:

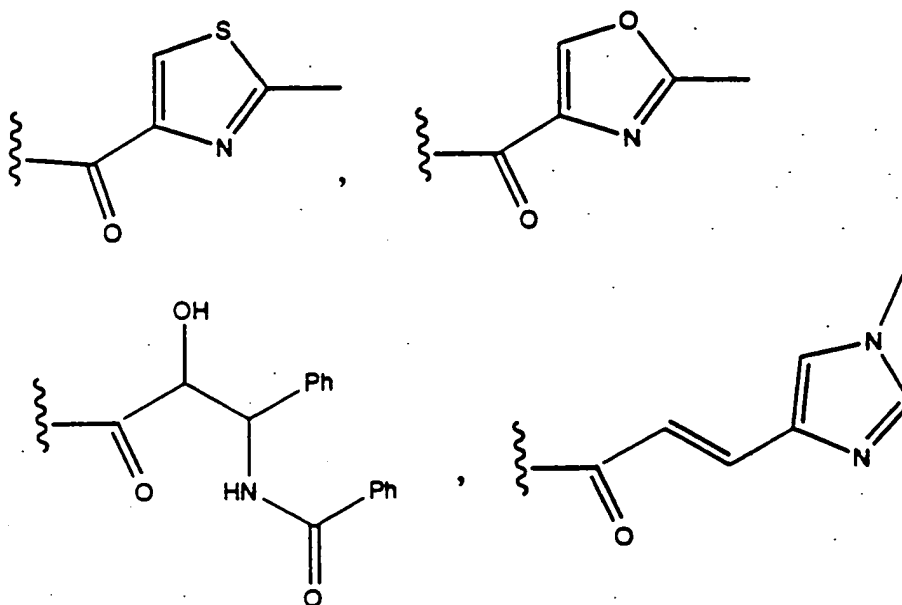


wherein R_2 is selected from the group consisting of
 hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
 acetyl, benzoyl, and tert-butoxycarbonyl.

42. An epothilone analog intermediate represented
 by the following structure:

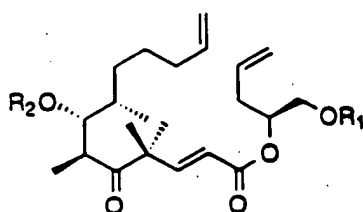


wherein R_1 is selected from the group consisting of
 hydrogen, tert-butyldiphenylsilyl, tert-
 butyldimethylsilyl, trimethylsilyl, methyl, acetyl,
 benzoyl, tert-butoxycarbonyl and the group represented by
 the formula:

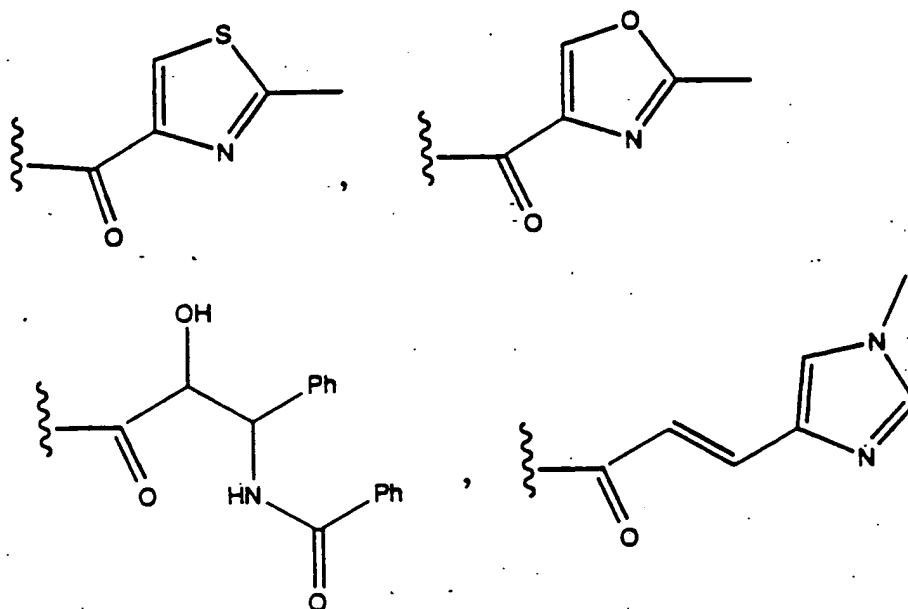


wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

43. An epothilone analog intermediate represented by the following structure:

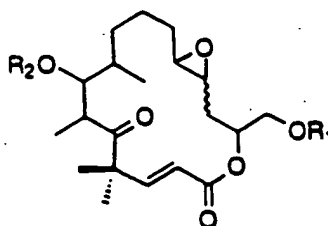


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:

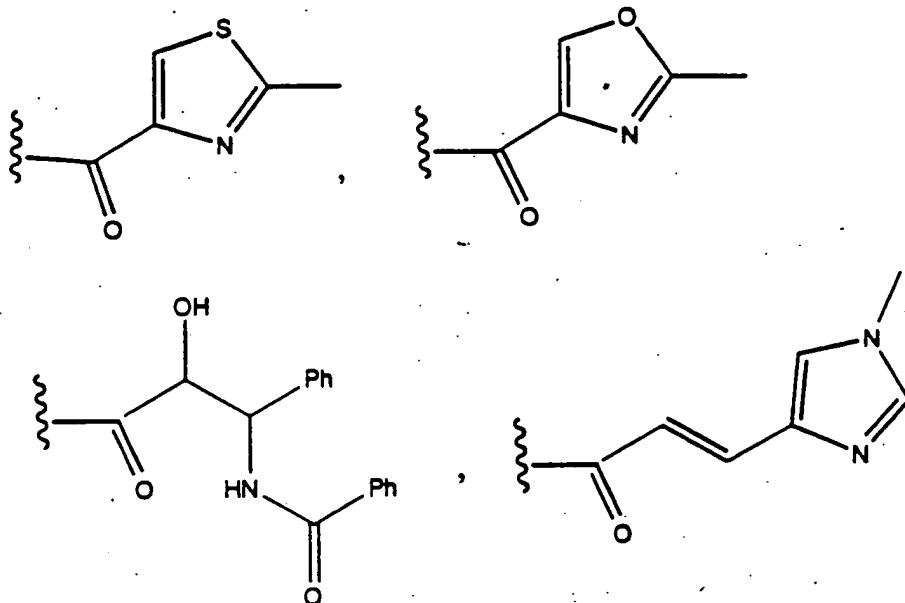


wherein R_2 is selected from the group consisting of, hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

44. An epothilone analog represented by the following structure:

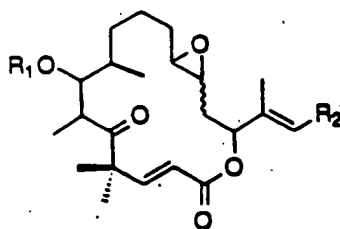


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:



wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

45. An epothilone analog represented by the following structure:

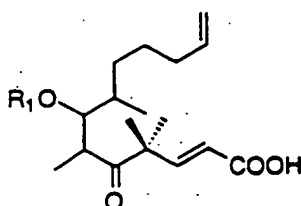


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group represented by the following structures:



5

46. An epothilone analog intermediate represented by the following structure:

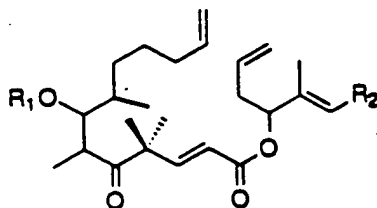


10

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

15

47. An epothilone analog intermediate represented by the following structure:

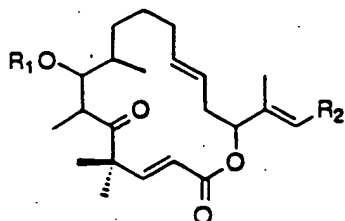


20

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group represented by the following structures:



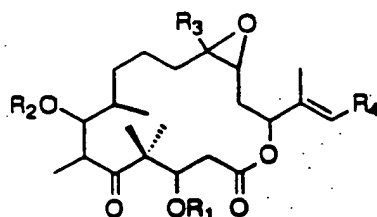
48. An epothilone analog intermediate represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group represented by the following structures:

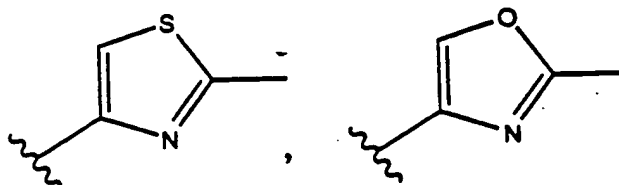


49. An epothilone analog represented by the following structure:

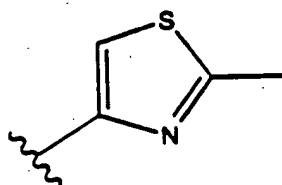


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group

represented by the formulas:

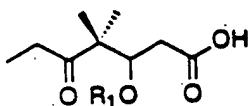


5 with the proviso that if R_3 is selected from the group consisting of methyl and hydrogen and R_4 is represented by the formula:



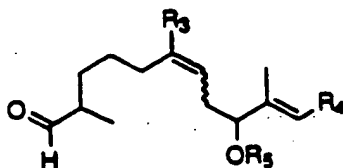
10 then R_1 and R_2 cannot be simultaneously hydrogen.

15 50. An epothilone analog intermediate represented by the following structure:



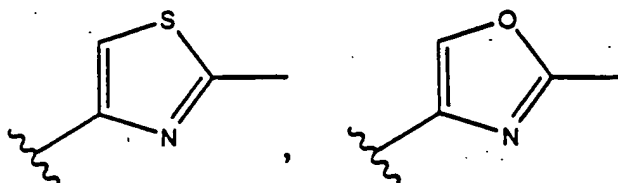
20 wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

25 51. An epothilone analog intermediate represented by the following structure:



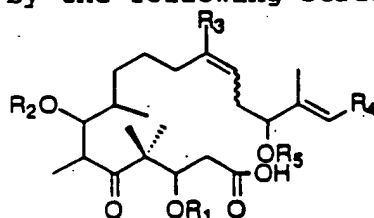
wherein R_3 is selected from the group consisting of

hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:



and wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl.

52. An epothilone analog intermediate represented by the following structure:



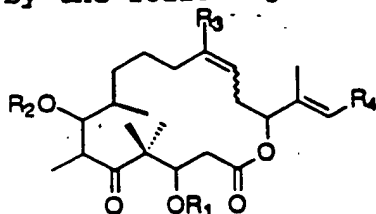
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:



and wherein R_5 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl and trimethylsilyl.

53. An epothilone analog intermediate represented

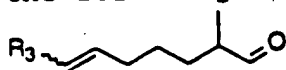
by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:

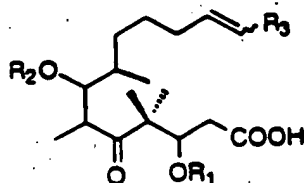


54. An epothilone analog intermediate represented by the following structure:



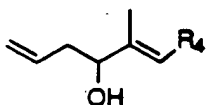
wherein R_3 is selected from the group consisting of hydrogen and $(\text{CH}_2)_n$ - (solid phase support).

55. An epothilone analog intermediate represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl and wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$ - (solid phase support).

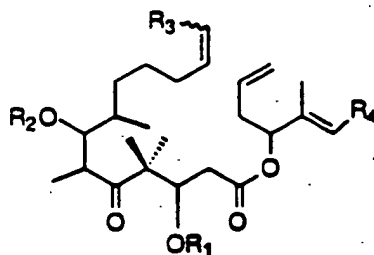
56. An epothilone analog intermediate represented by the following structure:



wherein R_4 is selected from the group represented by the formulas:

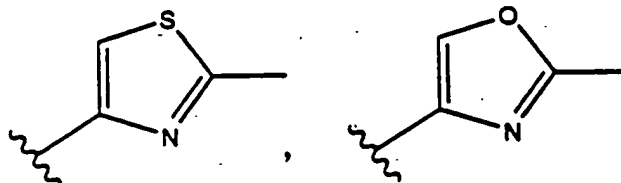


57. An epothilone analog intermediate represented by the following structure:



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected

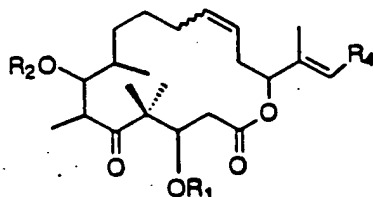
from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:



5

58. An epothilone analog intermediate represented by the following structure:

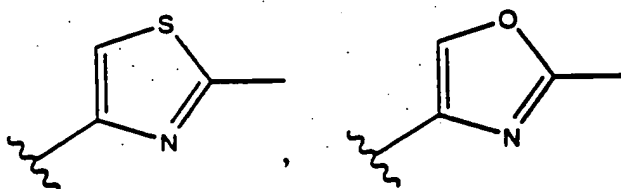
10



wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:

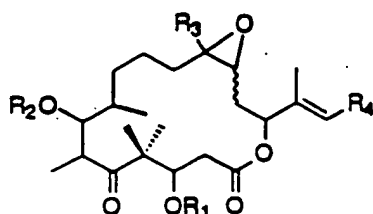
15

20

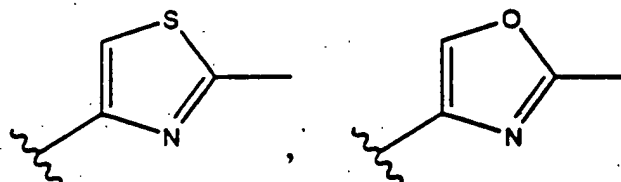


59. A method for synthesizing an epothilone analog represented by the following structure:

25

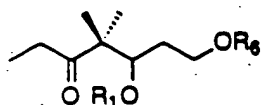


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:



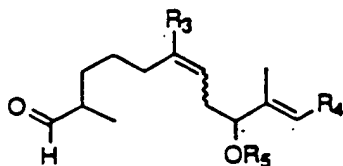
which comprises the following steps:

Step A: condensing a keto acid represented by the following structure:

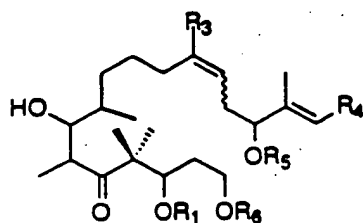


wherein R_6 is selected from the group consisting of tert-butyldimethylsilyl, trimethylsilyl, tert-butyldiphenylsilyl, methyl, hydrogen, triethylsilyl, and benzyl;

with an aldehyde represented by the following structure:

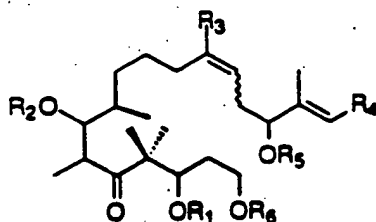


wherein R_5 is selected from the group consisting of tert-butyltrimethylsilyl and trimethylsilyl, for producing a β -hydroxy ketone with a free hydroxyl moiety and a R_6 protected hydroxyl moiety represented by the following structure:



; then

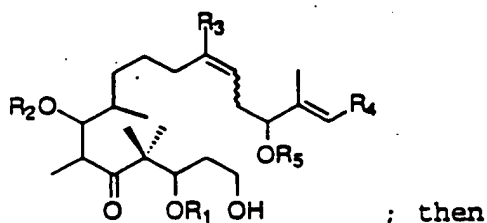
Step B: derivatizing the free hydroxyl moiety of said β -hydroxy ketone of Step A with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyltrimethylsilyl chloride, tert-butyltrimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxymino)-2-phenylacetonitrile for producing a derivatized β -hydroxy ketone represented by the following structure:



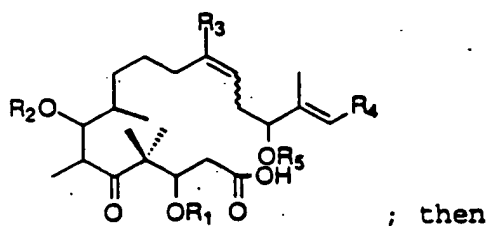
; then

Step C: regioselectively deprotecting the R_6 protected hydroxyl moiety of the derivatized β -hydroxy ketone of said step B for producing a terminal alcohol

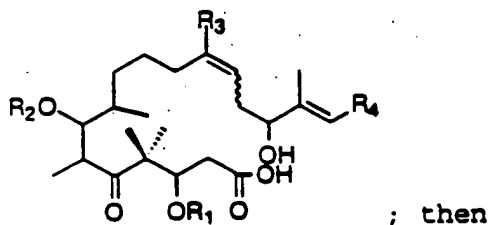
with the following structure:



5 Step D: oxidizing the terminal alcohol of said Step C for producing a derivatized carboxylic acid with a R₅ protected hydroxyl moiety with the following structure:

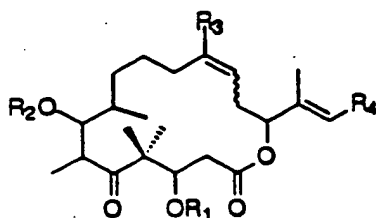


10 Step E: regioselectively deprotecting the R₅ protected hydroxyl moiety of the derivatized carboxylic acid of said step D for producing a hydroxy acid with the following structure:



15 Step F: macrolactonizing the hydroxy acid of said Step E for producing a macrolide with the following structure:

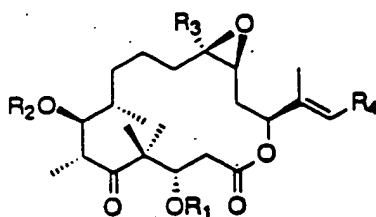
20



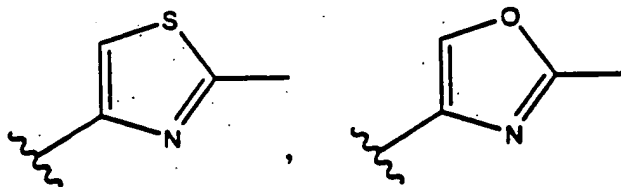
; and then

Step G: epoxidizing the macrolide of said Step F for producing the epothilone analog.

60. A method for synthesizing an epothilone analog represented by the following structure:

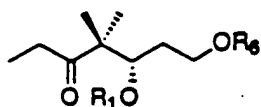


wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, and $-\text{CH}_2\text{CO}_2\text{H}$; wherein R_4 is selected from the group represented by the formulas:



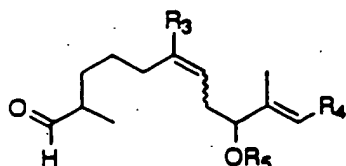
which comprises the following steps:

Step A: condensing a keto acid represented by the following structure:

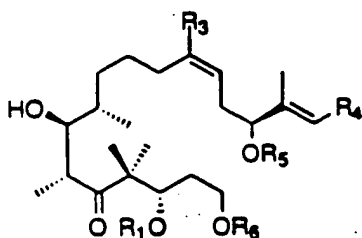


wherein R_6 is selected from the group consisting of tert-butyl-
 5 butyldimethylsilyl, trimethylsilyl, tert-butyl-
 diphenylsilyl, methyl, hydrogen, triethylsilyl, and
 benzyl;

with an aldehyde represented by the following structure:

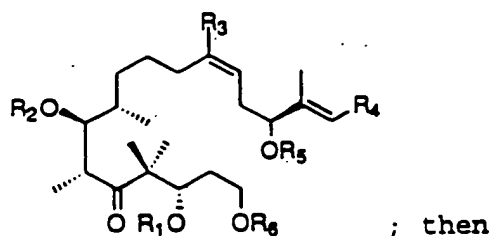


wherein R_5 is selected from the group consisting of tert-
 15 butyldimethylsilyl and trimethylsilyl, for producing a β -
 hydroxy ketone with a free hydroxyl moiety and a R_6 ,
 protected hydroxyl moiety represented by the following
 structure:

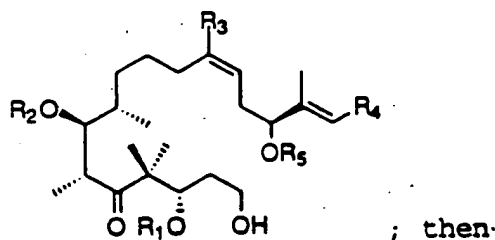


; then

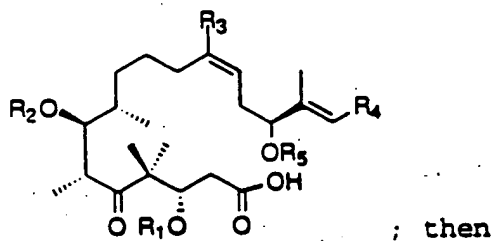
Step B: derivatizing the free hydroxyl moiety of
 said β -hydroxy ketone of Step A with a derivatizing agent
 represented by the formula R_2-X wherein R_2-X is selected
 25 from the group consisting of tert-butyl-
 dimethylsilyl chloride, tert-butyl-
 dimethylsilyl triflate, trimethylsilyl
 chloride, trimethylsilyl triflate, methyl
 iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride,
 benzoic acid, benzoyl chloride, and 2-(tert-
 30 butoxycarbonyloxyimino)-2-phenylacetonitrile for producing
 a derivatized β -hydroxy ketone represented by the
 following structure:



5 Step C: regioselectively deprotecting the R_6 protected hydroxyl moiety of the derivatized β -hydroxy ketone of said step B for producing a terminal alcohol with the following structure:

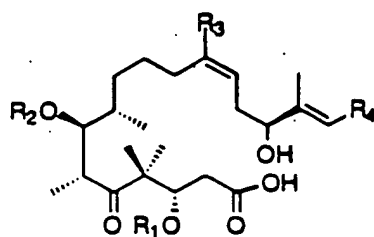


10 Step D: oxidizing the terminal alcohol of said Step C for producing a derivatized carboxylic acid with a R_5 protected hydroxyl moiety with the following structure:



15 Step E: regioselectively deprotecting the R_5 protected hydroxyl moiety of the derivatized carboxylic acid of said step D for producing a hydroxy acid with the following structure:

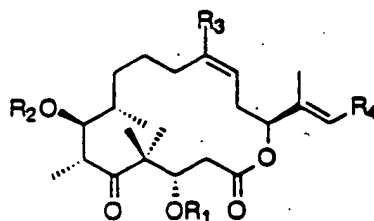
20



; then

Step F: macrolactonizing the hydroxy acid of said Step E for producing a macrolide with the following structure:

5



; and then

Step G: epoxidizing the macrolide of said Step F for producing the epothilone analog.

10

Abstract of the Disclosure

5 Epothilone A, epothilone B, analogs of epothilone and
libraries of epothilone analogs are synthesized. Epothilone A
and B are known anticancer agents that derive their anticancer
activity by the prevention of mitosis through the induction and
stabilization of microtubulin assembly. The analogs of
epothilone are novel. Several of the analogs are demonstrated to
have a superior cytotoxic activities as compared to epothilone A
0 or epothilone B as demonstrated by their enhanced ability to
induce the polymerization and stabilization of microtubules.

PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated next to my name in Part A of page 2 hereof.

I believe I am the original, first, and sole inventor (if only one name is listed) or original, first, and joint inventor (if plural names are listed) of the subject matter which is claimed and for which a patent is sought on the invention entitled PROCESS AND SOLUTION PHASE SYNTHESIS OF EPOTHILONES A AND B AND LIBRARIES OF EPOTHILONE LOGS the specification of which:

_____ is attached hereto

☒ was filed on May 14, 1997 as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 for any foreign application(s) for patent or inventor's certificate listed in PART B on page 2 hereof and have also identified in PART B on page 2 hereof any foreign application for patent or inventor's certificate having a filing date before that of this application on which priority is claimed.

I hereby claim the benefit under Title 35, United States Code, Sec. 120 of any United States application(s) listed in PART C on page 2 hereof and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Sec. 112, I acknowledge the duty to disclose material information as required in Title 37, Code of Federal Regulations, Sec. 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the same so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may invalidate the validity of the application or any patent issued thereon.

I hereby appoint the following as my attorneys or agents with full power of substitution to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith:

Glas A. Bingham Reg. No. 32,457
Thomas Fitting Reg. No. 34,163

Donald G. Lewis Reg. No. 28,636
Emily Holmes Reg. No. P-40,652

My mailing address for this application is:

THE SCRIPPS RESEARCH INSTITUTE
10550 North Torrey Pines Road
Mail Drop TPC 8
La Jolla, California 92037

Pages 2 and 3 attached, signed, and made a part hereof.

PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

A: Inventor Information And Signature

name of SOLE or FIRST inventor Kyriacos Nicolaou
izenship _____ Post Office Address _____

dence (if different) _____

ntor's Signature: _____ Date: _____

name of SECOND joint inventor, if any Yun He
izenship _____ Post Office Address _____

dence (if different) _____

nd Inventor's Signature: _____ Date: _____

name of THIRD joint inventor, if any Sacha Ninkovic
izenship _____ Post Office Address _____

dence (if different) _____

d Inventor's Signature: _____ Date: _____

name of FOURTH joint inventor, if any Joaquin Pastor
izenship _____ Post Office Address _____

dence (if different) _____

th Inventor's Signature: _____ Date: _____

name of FIFTH joint inventor, if any Frank Roschangar
izenship _____ Post Office Address _____

dence (if different) _____

h Inventor's Signature: _____ Date: _____

name of SIXTH joint inventor, if any Francisco Sarabia
izenship _____ Post Office Address _____

dence (if different) _____

h Inventor's Signature: _____ Date: _____

Page 1 to which this is attached and from which this Page 2 continues.

name of SEVENTH joint inventor, if any Hans Vallberg
izenship _____ Post Office Address _____

idence (if different) _____

enth Inventor's Signature: _____ Date: _____

name of EIGHTH joint inventor, if any Dionisios Vourloumis
izenship _____ Post Office Address _____

idence (if different) _____

th Inventor's Signature: _____ Date: _____

name of NINTH joint inventor, if any Nicolas Winssinger
izenship _____ Post Office Address _____

idence (if different) _____

th Inventor's Signature: _____ Date: _____

l name of TENTH joint inventor, if any Zhen Yang
izenship _____ Post Office Address _____

idence (if different) _____

th Inventor's Signature: _____ Date: _____

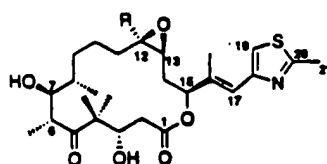
R B: Prior Foreign Application(s)

ial No.	Country	Day/Month/Year Filed	Priority Claimed
			<input type="checkbox"/> Yes <input type="checkbox"/> No

R C: Claim For Benefit of Filing Date of Earlier U.S. Application(s)

ial No.	Filing Date	Status:
032,864	12/13/96	<input type="checkbox"/> Patented <input checked="" type="checkbox"/> Pending <input type="checkbox"/> Abandoned

Pages 1 and 2 to which this is attached and from which this Page 3 continues.



- 1: R = H, epothilone A
2: R = Me, epothilone B

FIGURE 1

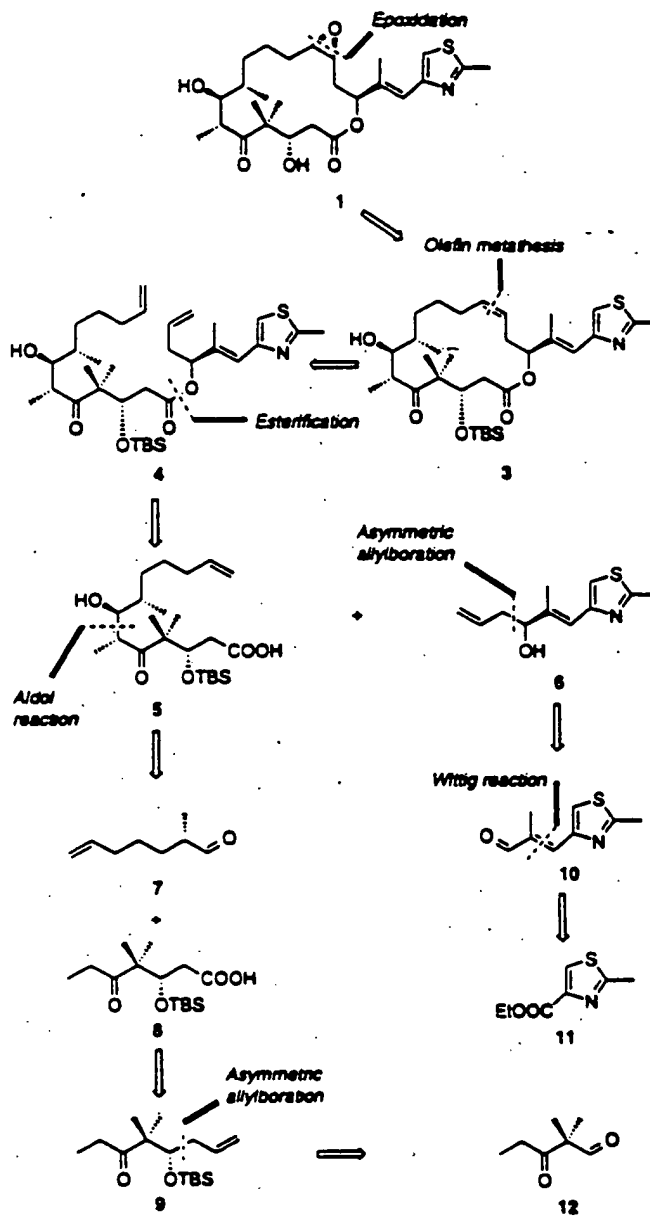


FIGURE 2

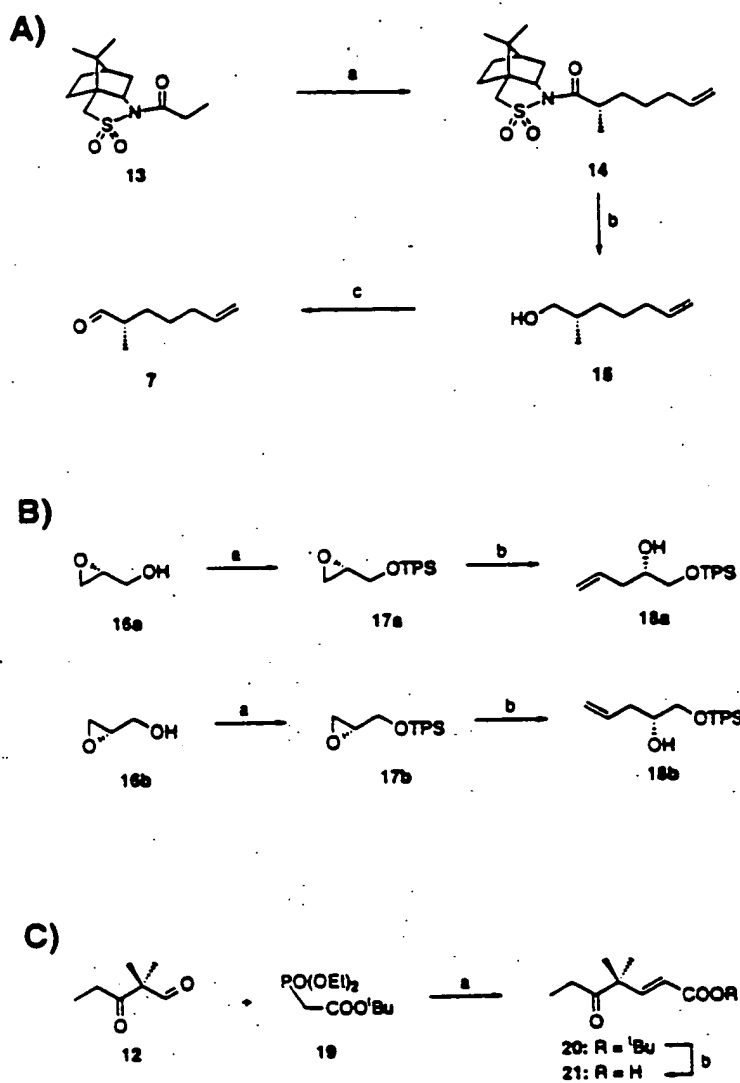


FIGURE 3

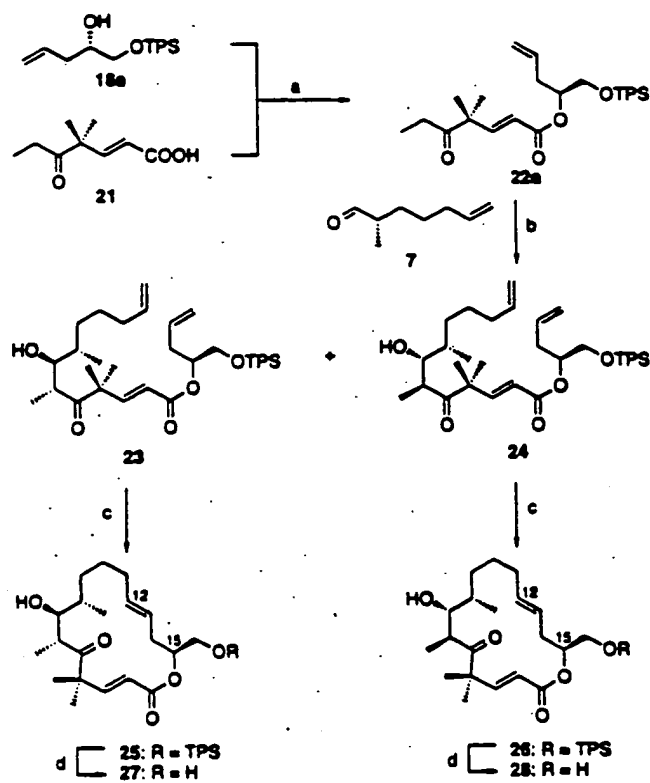


FIGURE 4

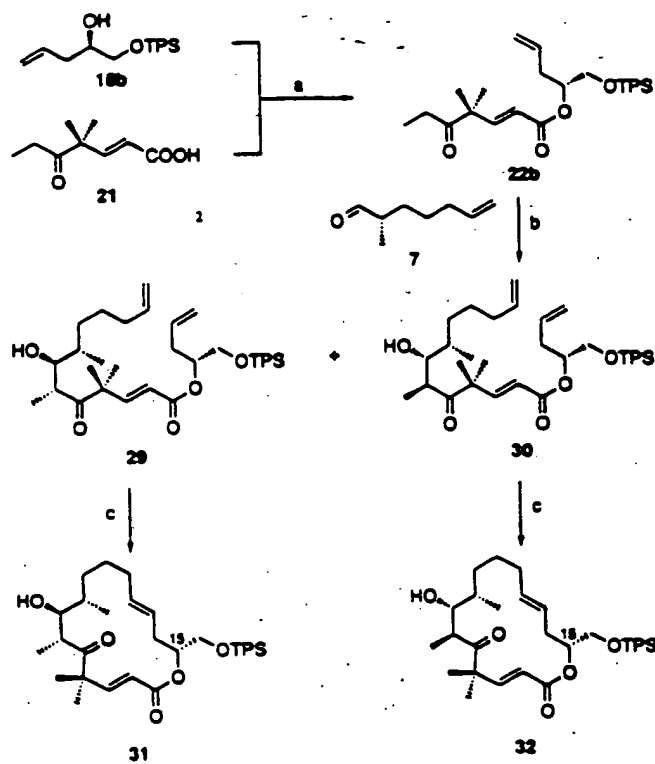


FIGURE 5

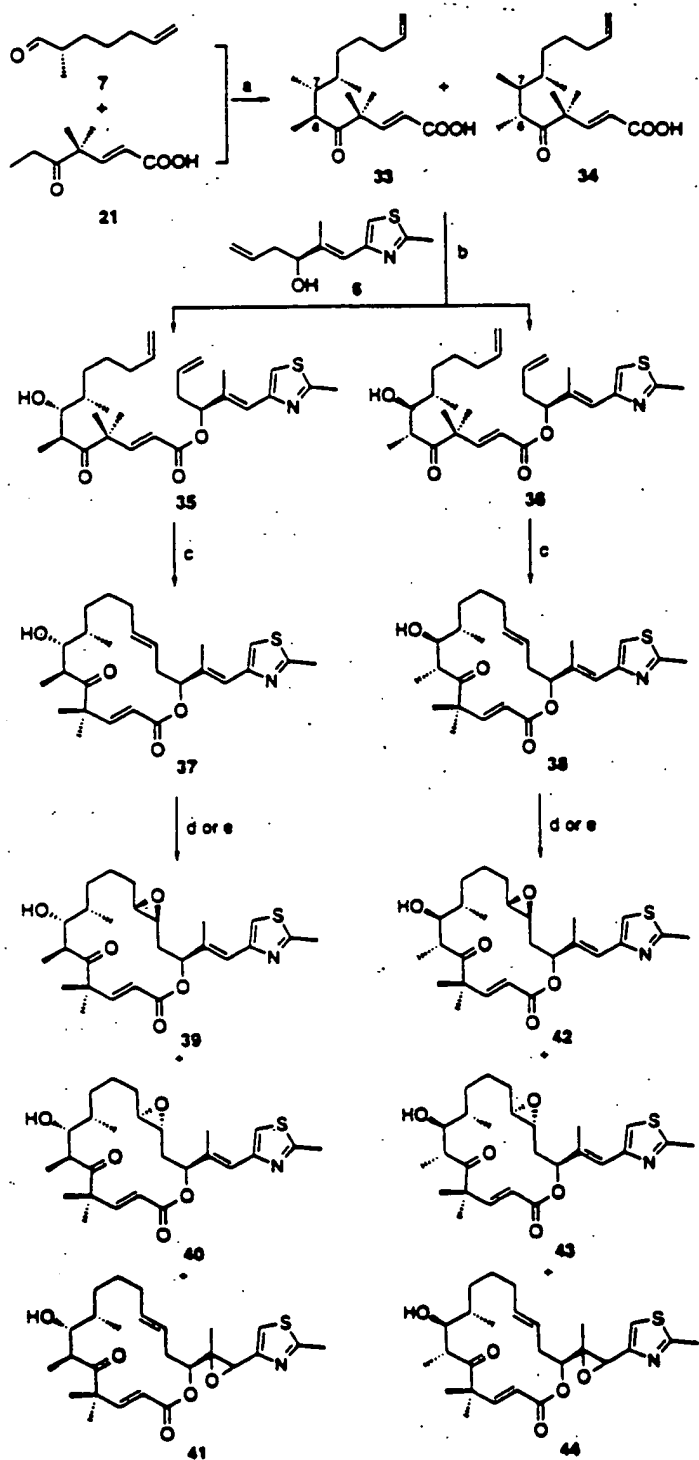


FIGURE 6

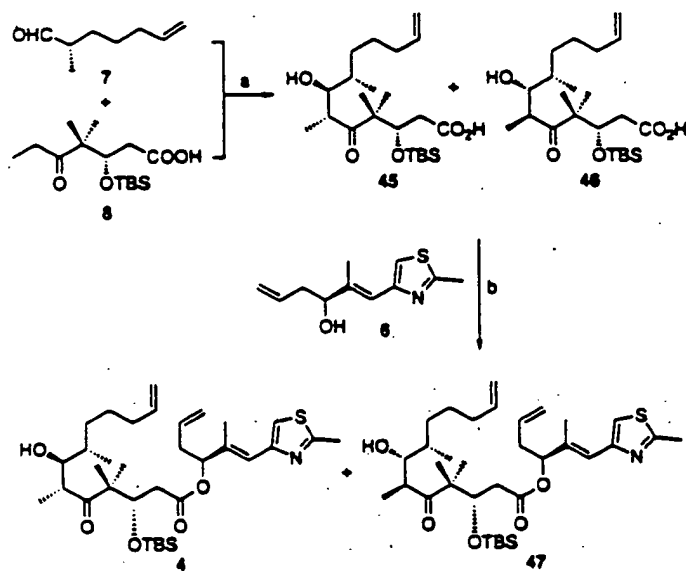


FIGURE 7

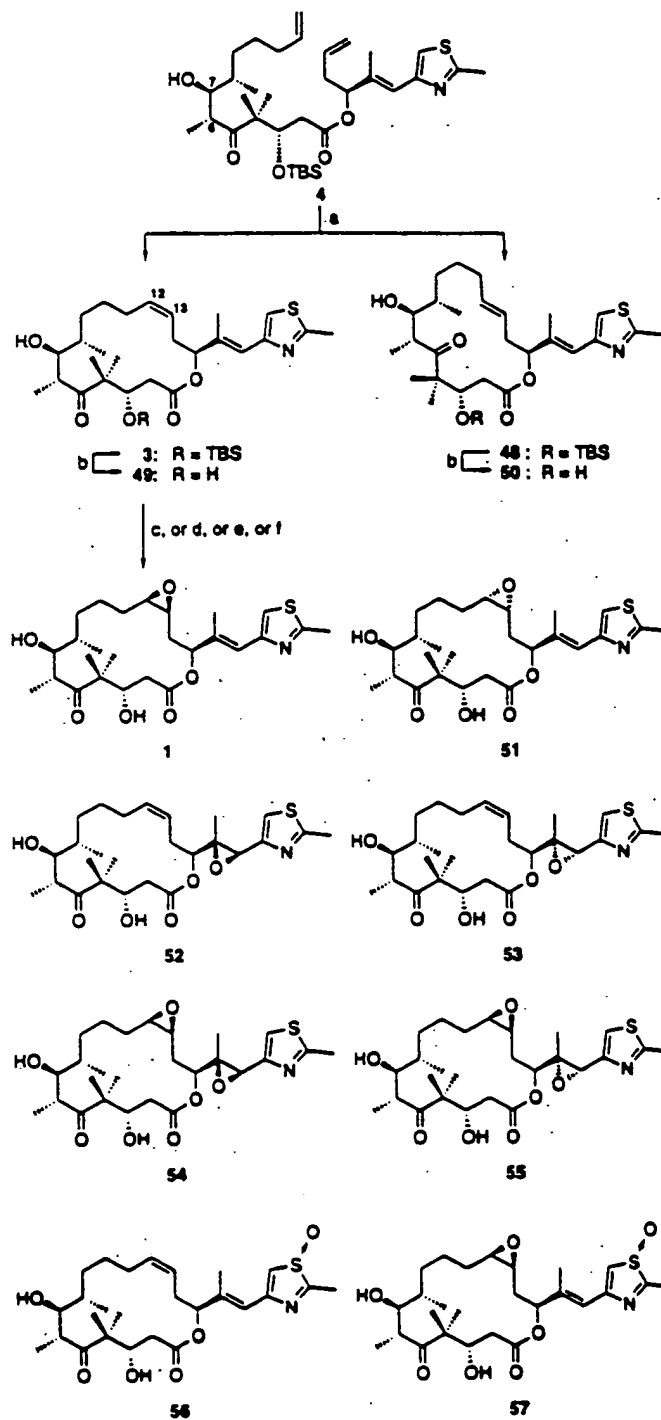


FIGURE 8

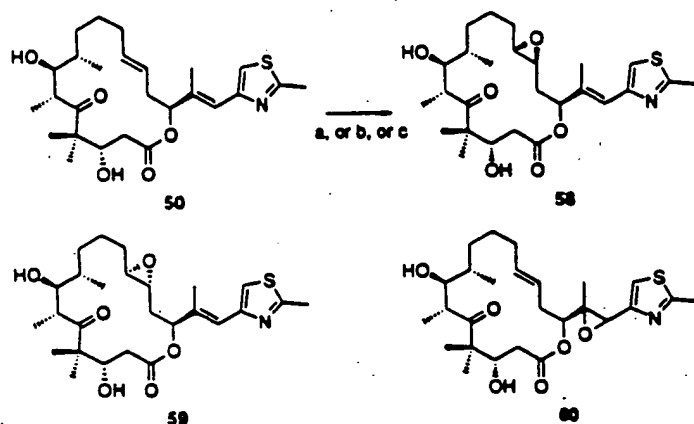


FIGURE 9

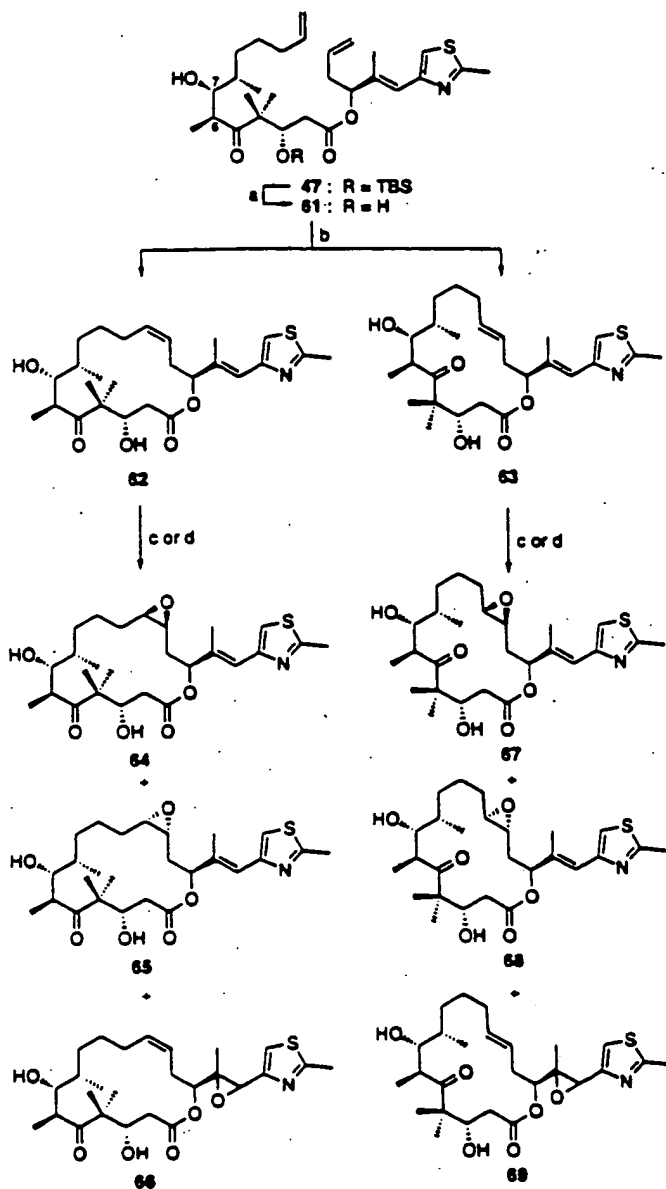


FIGURE 10

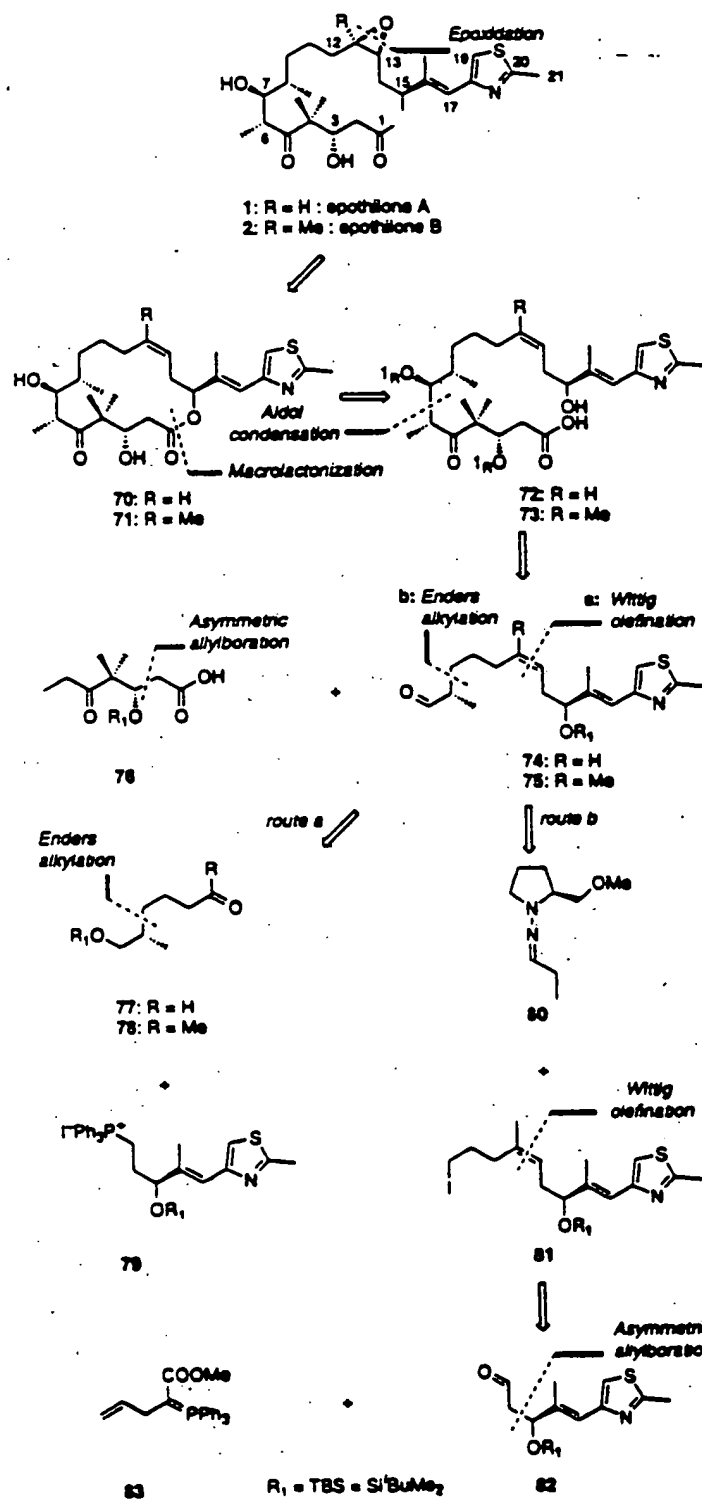


FIGURE 11

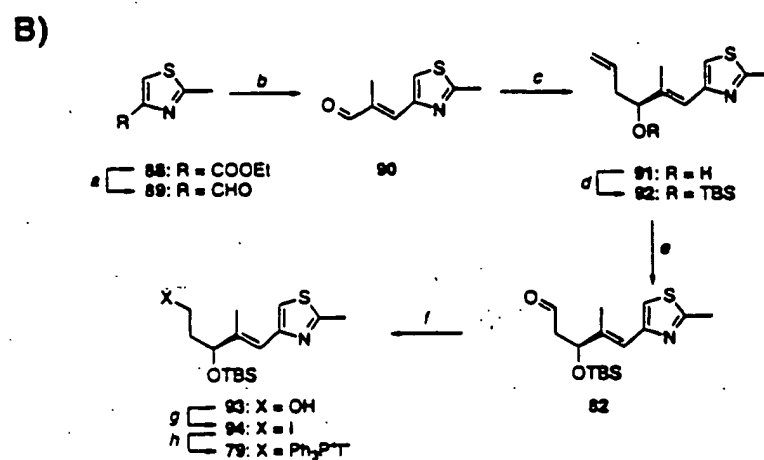
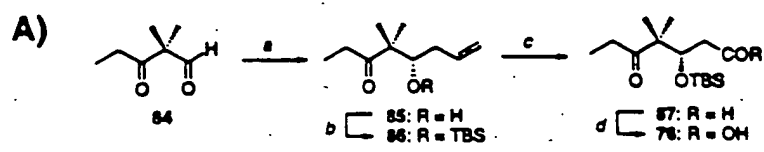


FIGURE 12

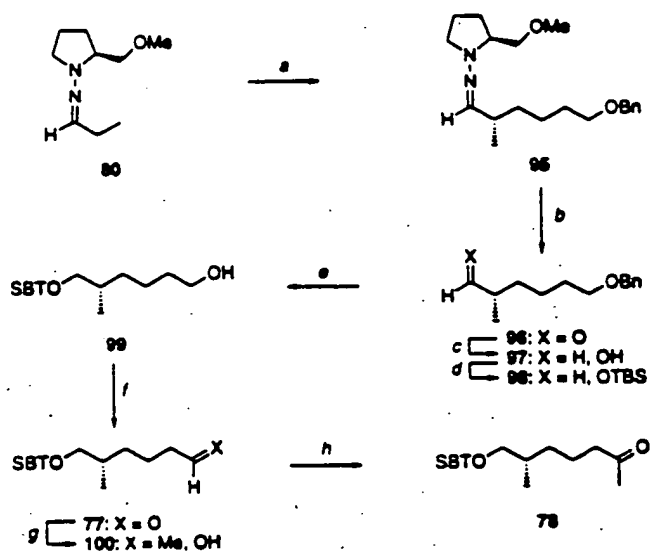


FIGURE 13

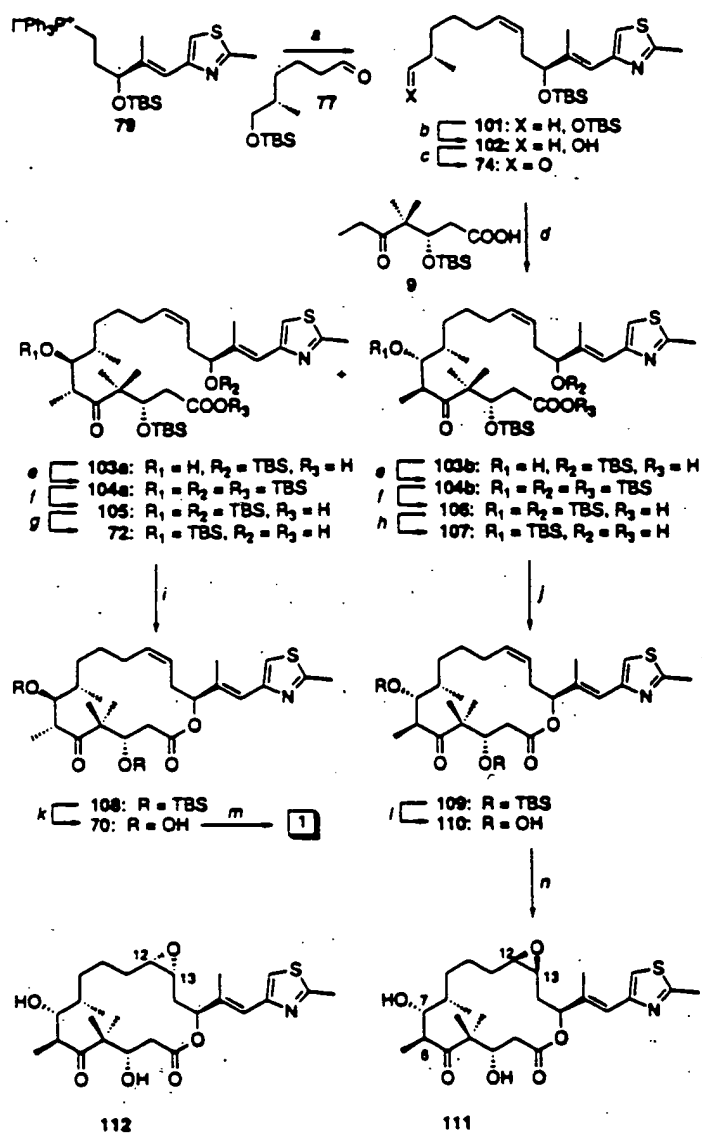


FIGURE 14

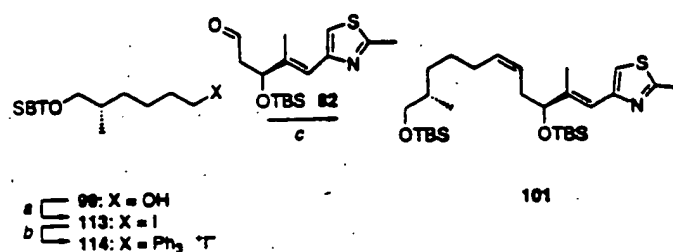


FIGURE 15

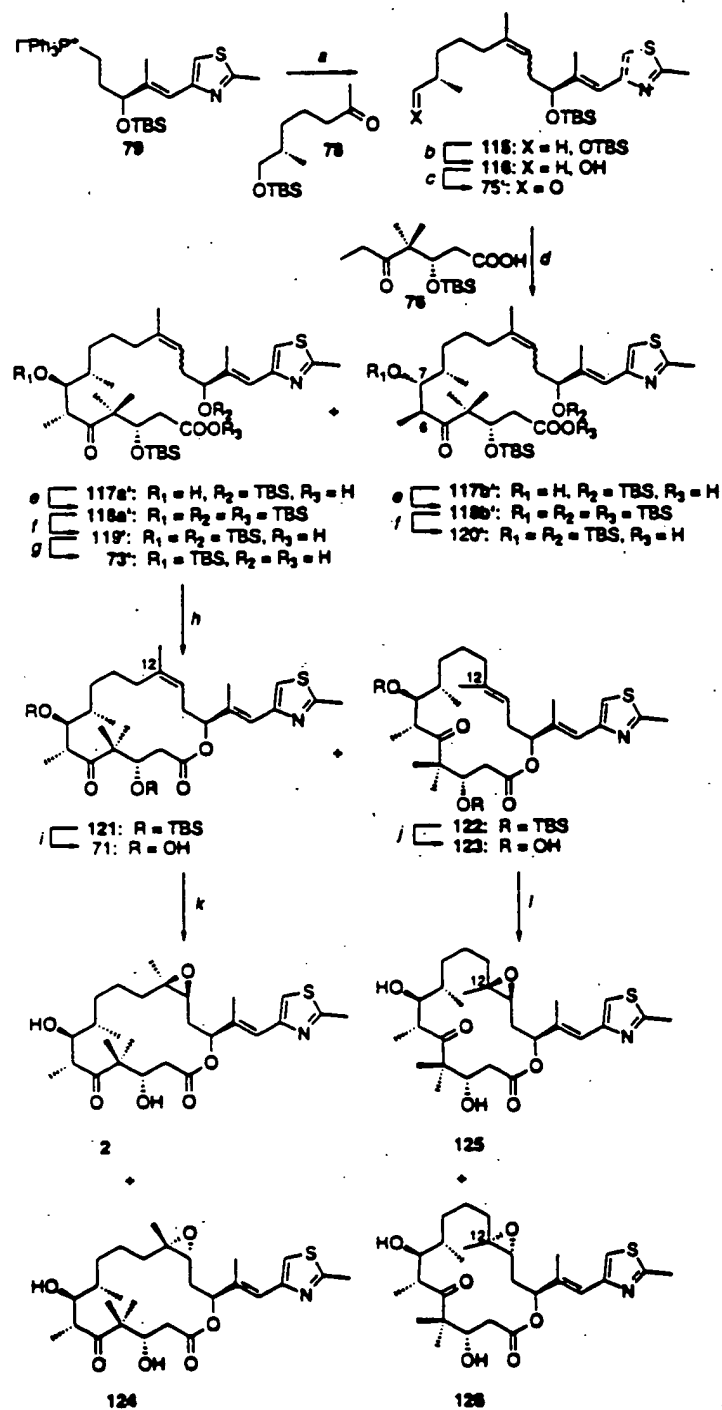


FIGURE 16

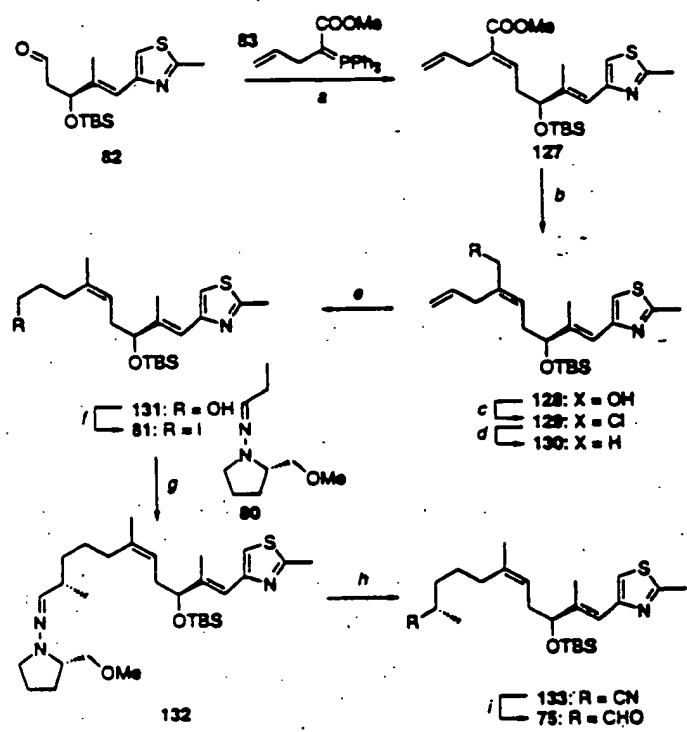


FIGURE 17

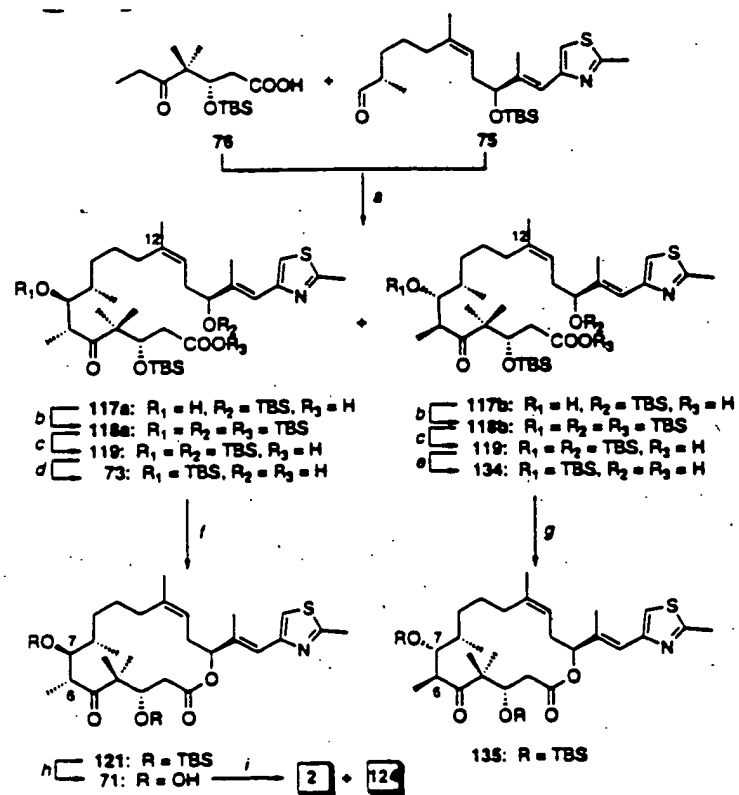


FIGURE 18

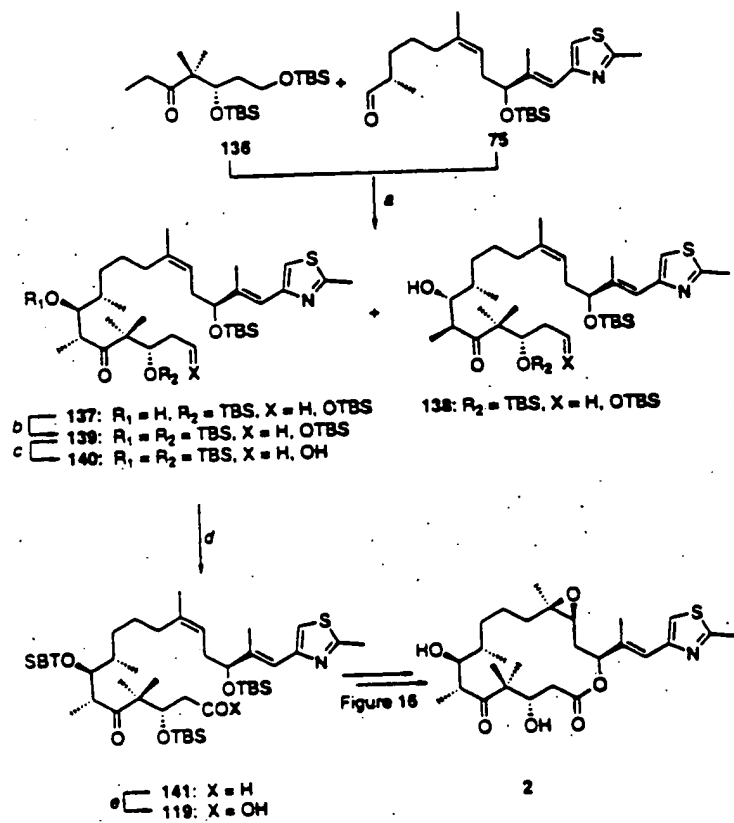


FIGURE 19

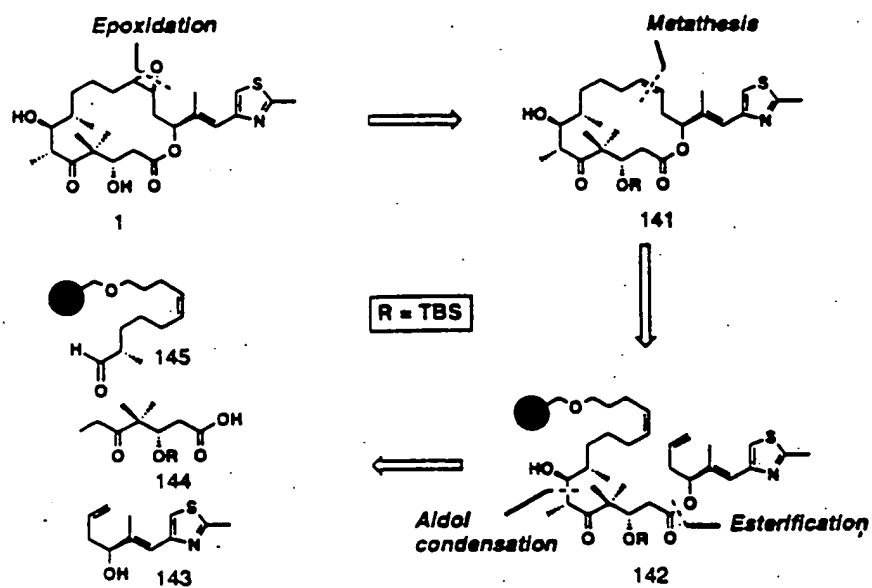


FIGURE 20

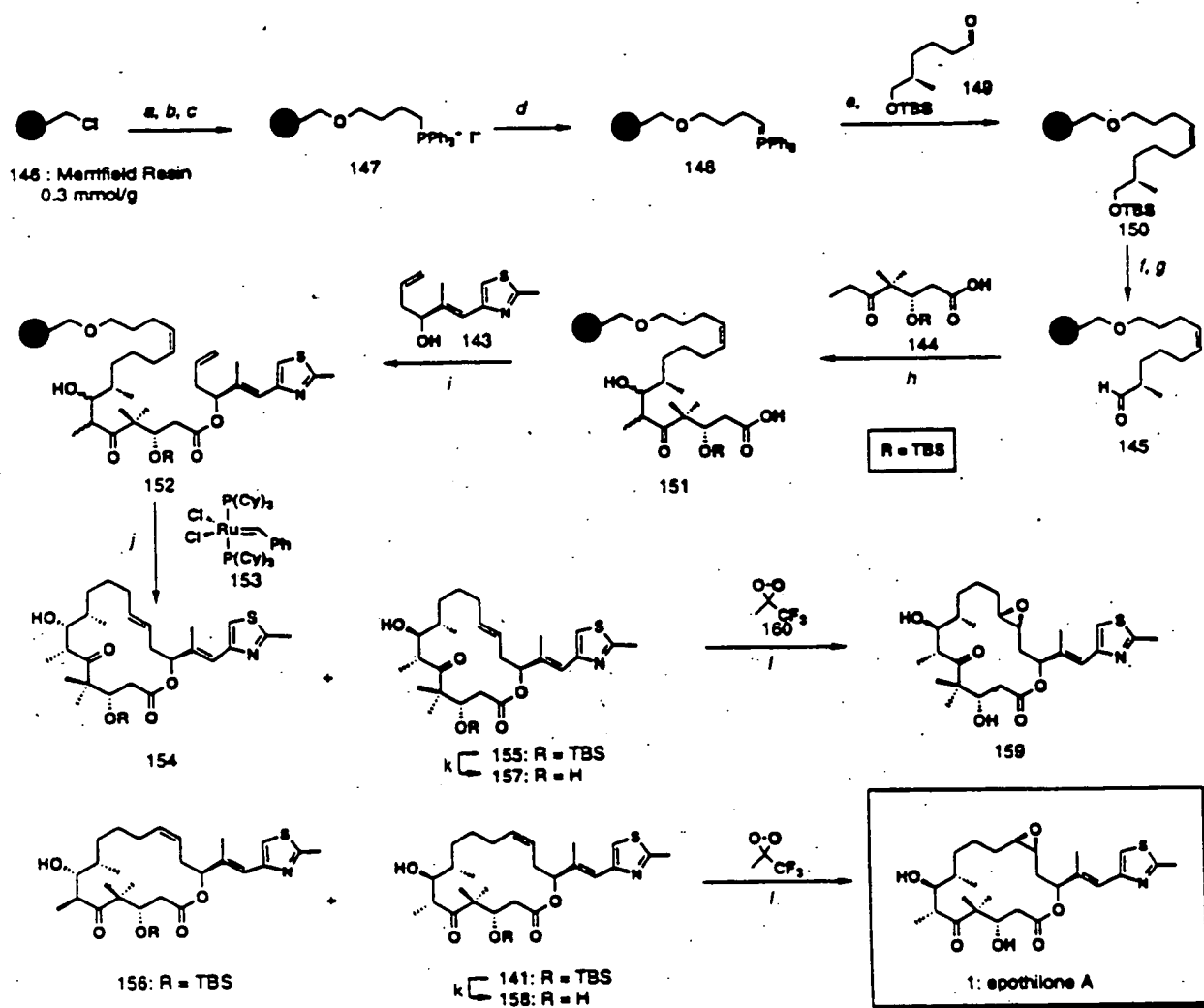


FIGURE 21

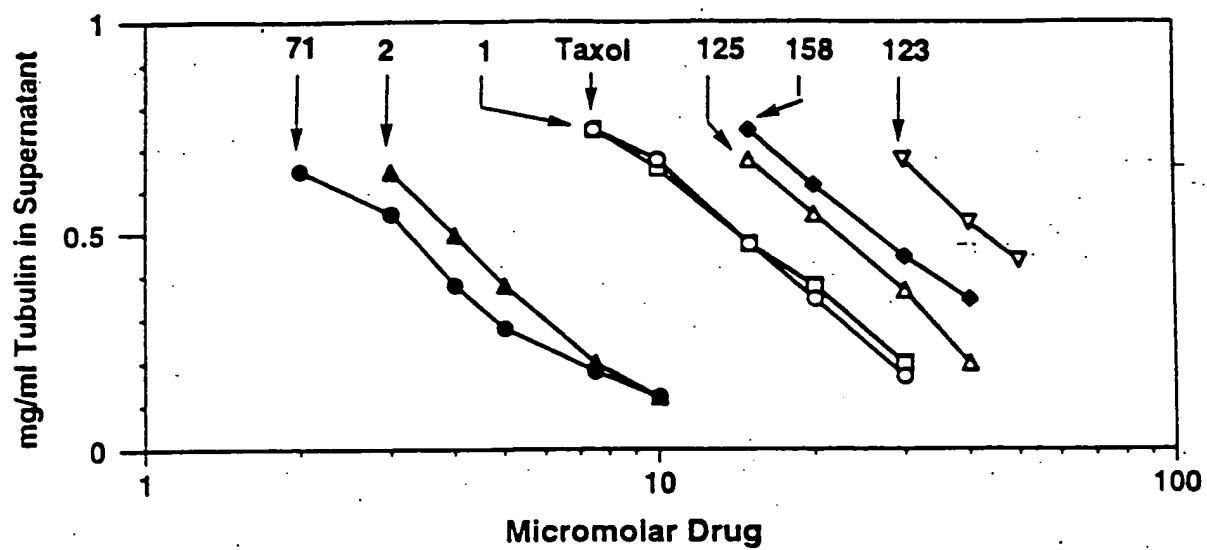
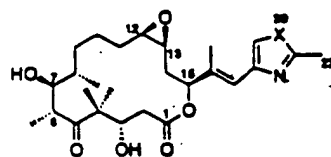


FIGURE 22

Compound	Induction of tubulin assembly ^a	Inhibition of human ovarian carcinoma cell growth ^b							
		Parental	Taxol ^c -resistant						MDR-line
			β -tubulin mutants						
			IC ₅₀ nM (relative resistance)						
EC ₅₀ (mM) \pm s.d.	1A9	1A9PTX10	1A9PTX22	A2780AD					
1	14 \pm 0.4	2.0	19 (9.5)	4.2 (2.1)	2.4 (1.2)				
2	4.0 \pm 0.1	0.040	0.035 (0.88)	0.045 (1.1)	0.040 (1.0)				
71	3.3 \pm 0.2	2.0	33 (17)	3.5 (1.8)	1.5 (0.80)				
158	25 \pm 1	25	>100 (>4)	75 (3.0)	22 (0.88)				
123	39 \pm 2	48	>100 (>2)	75 (1.6)	24 (0.50)				
125	22 \pm 0.9	3.5	30 (8.6)	5.5 (1.6)	3.0 (0.86)				
Taxol	15 \pm 2	2.0	50 (25)	43 (22)	>100 (>50)				

FIGURE 23



1: X = S: epothilone A
 161: X = O: epothilone A

Figure 24.

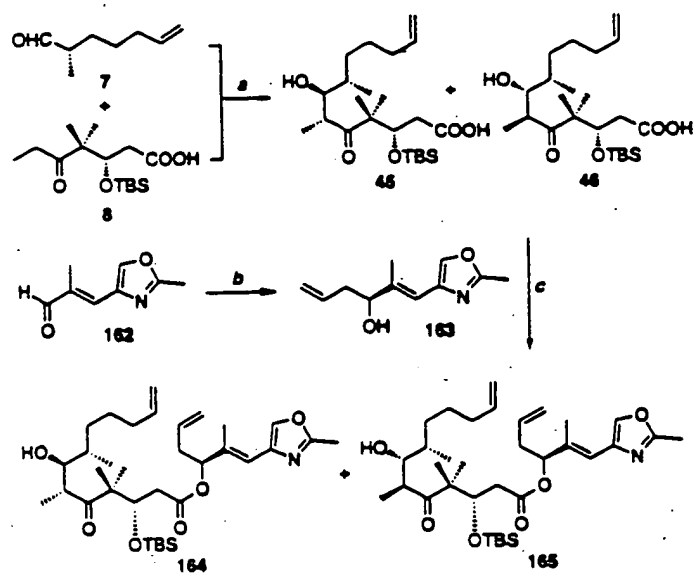


FIGURE 25

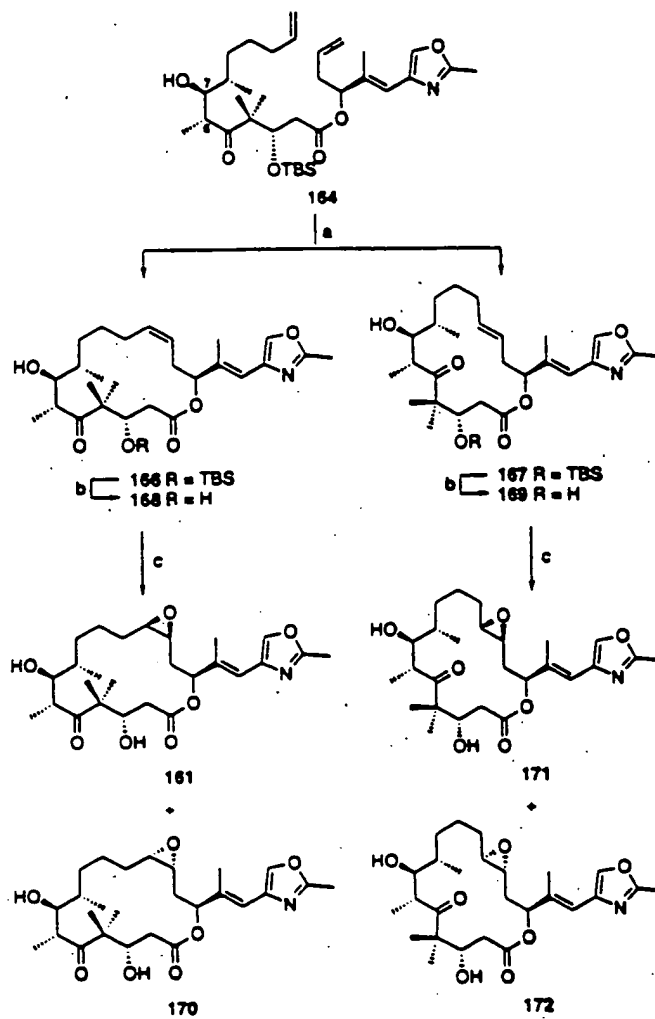


FIGURE 26

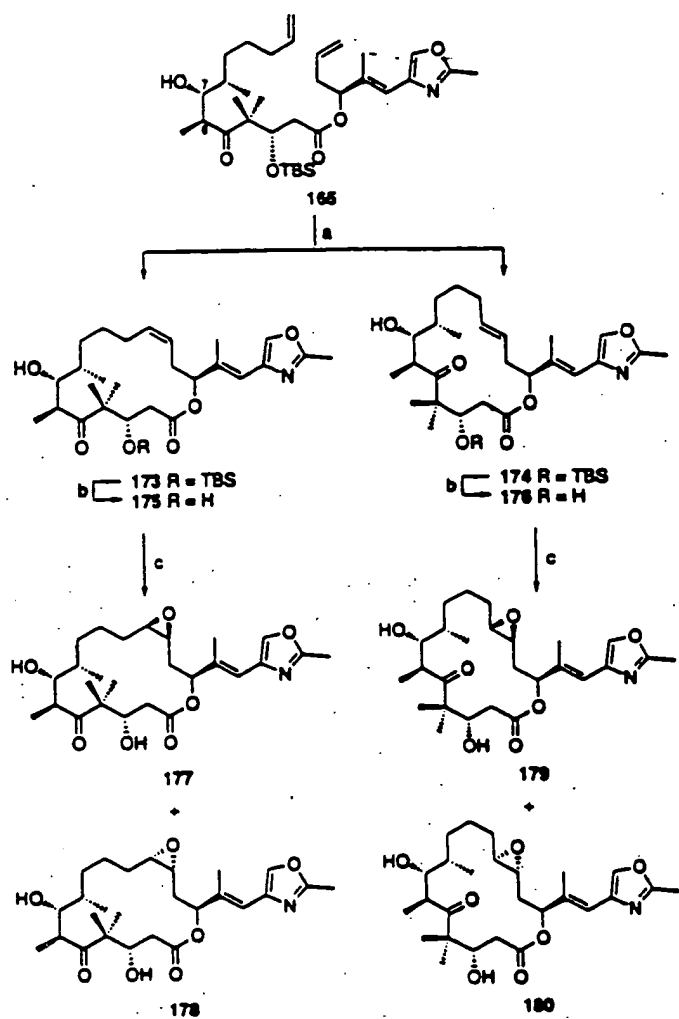


FIGURE 27

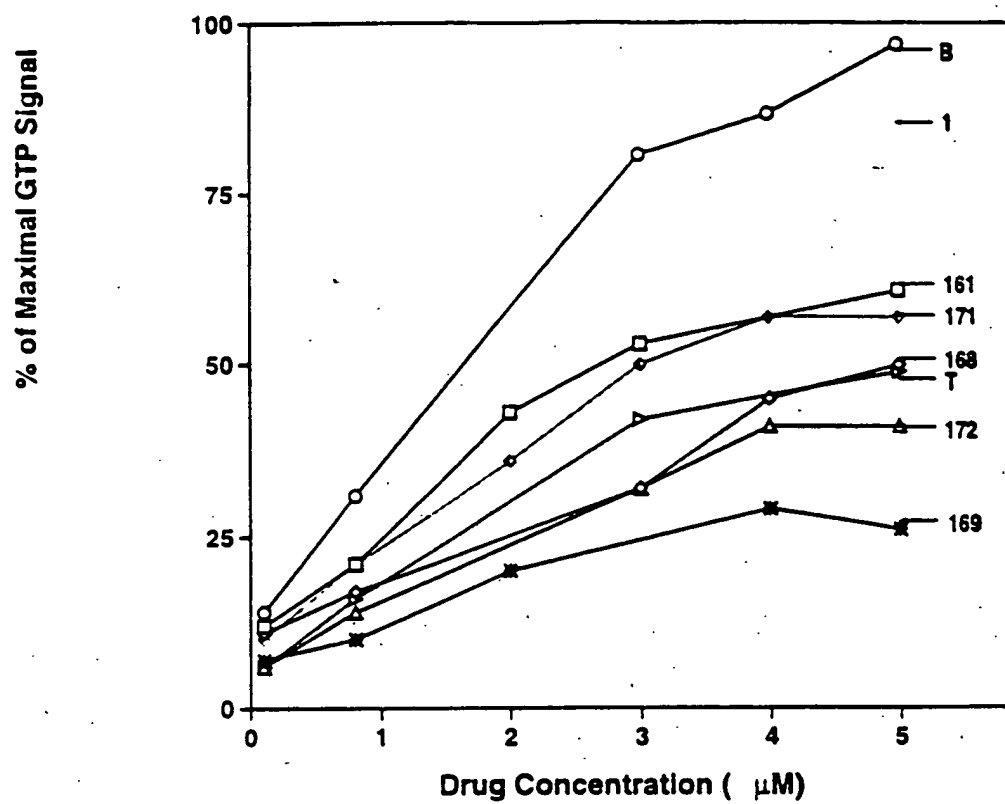


FIGURE 28

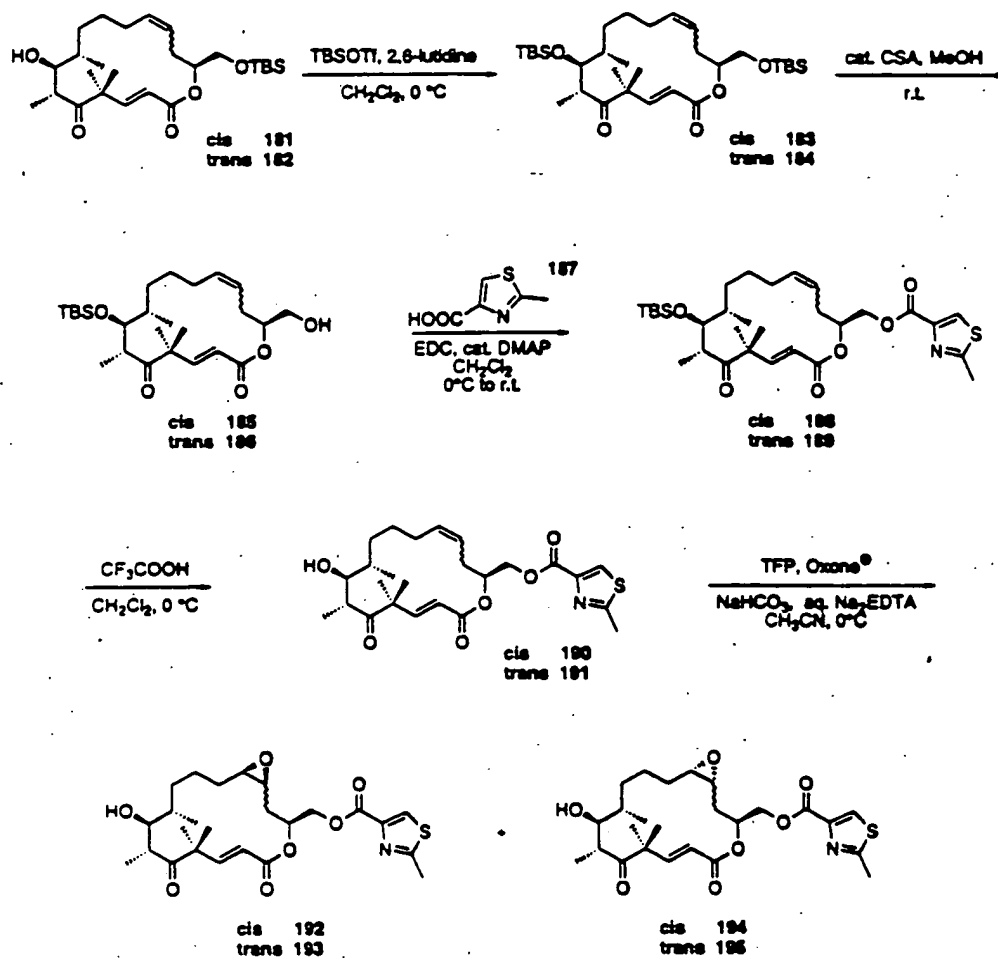


FIGURE 29

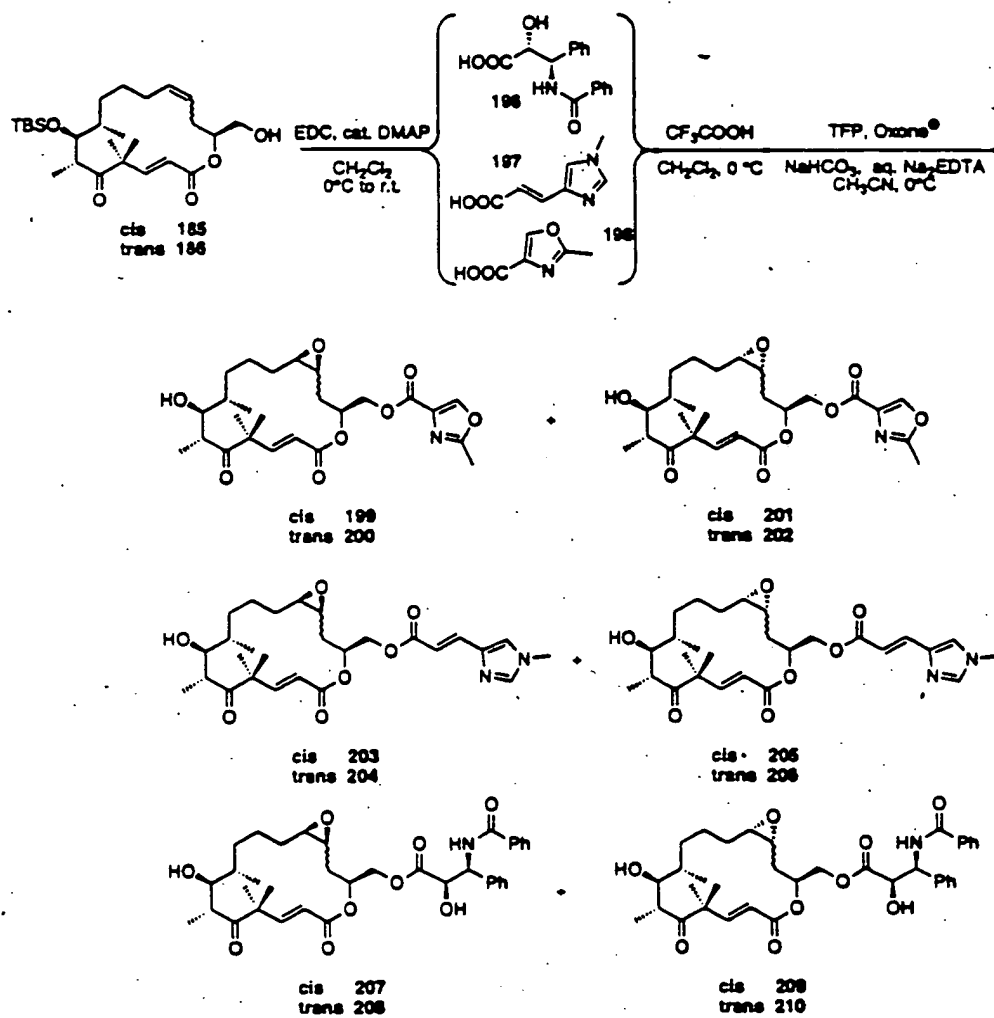


FIGURE 30

FIGURE

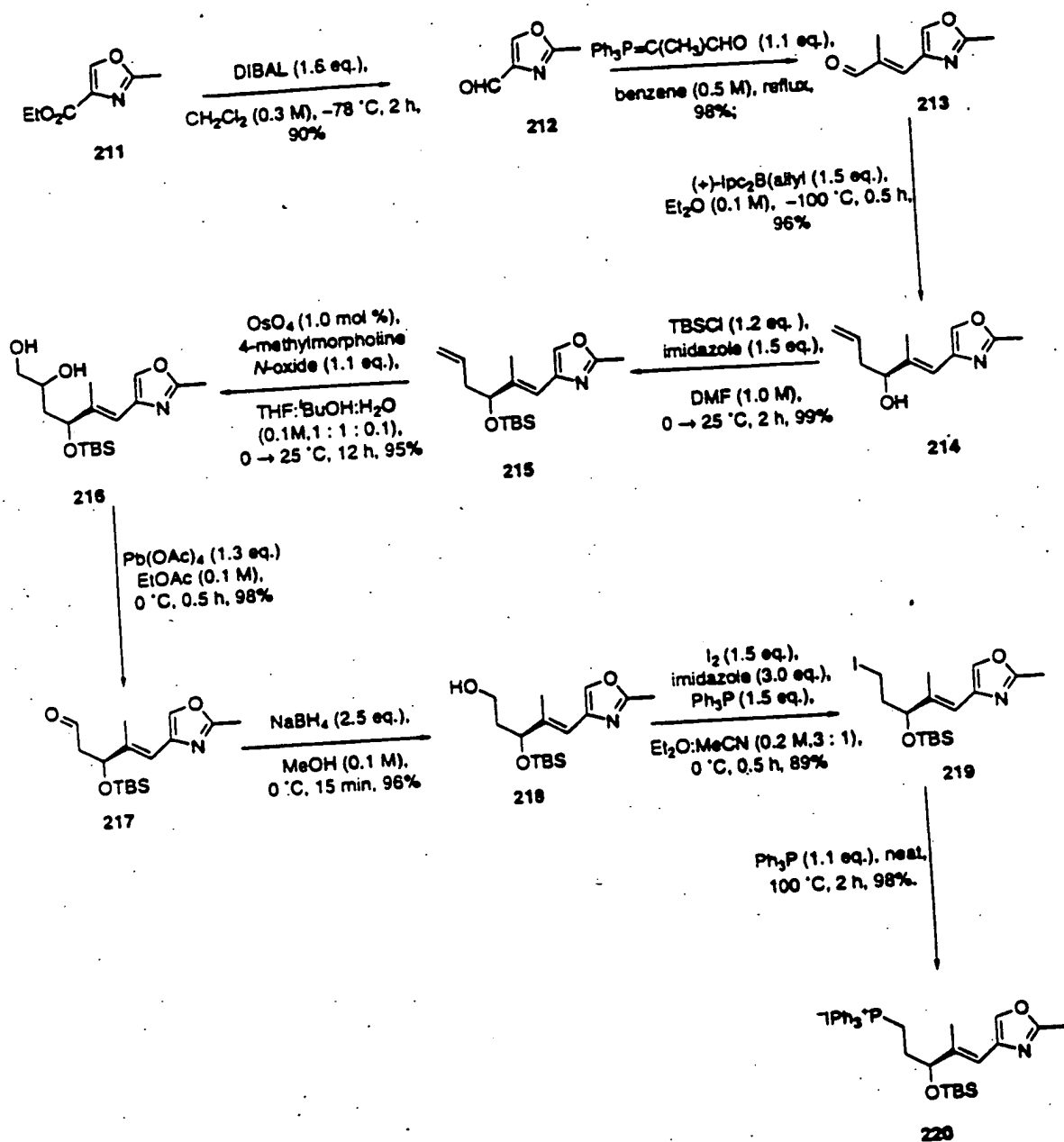


FIGURE 31



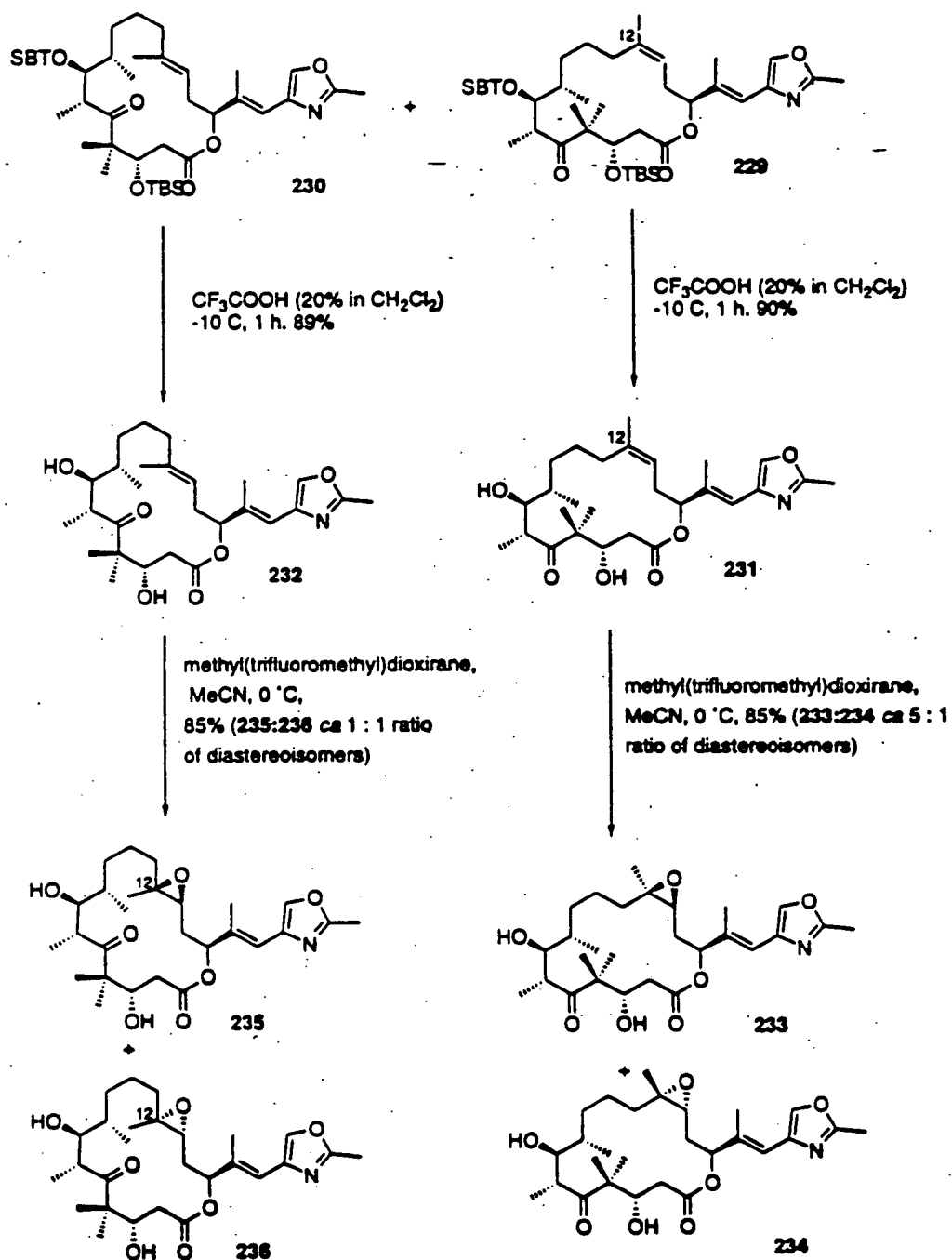


FIGURE 33

PRE



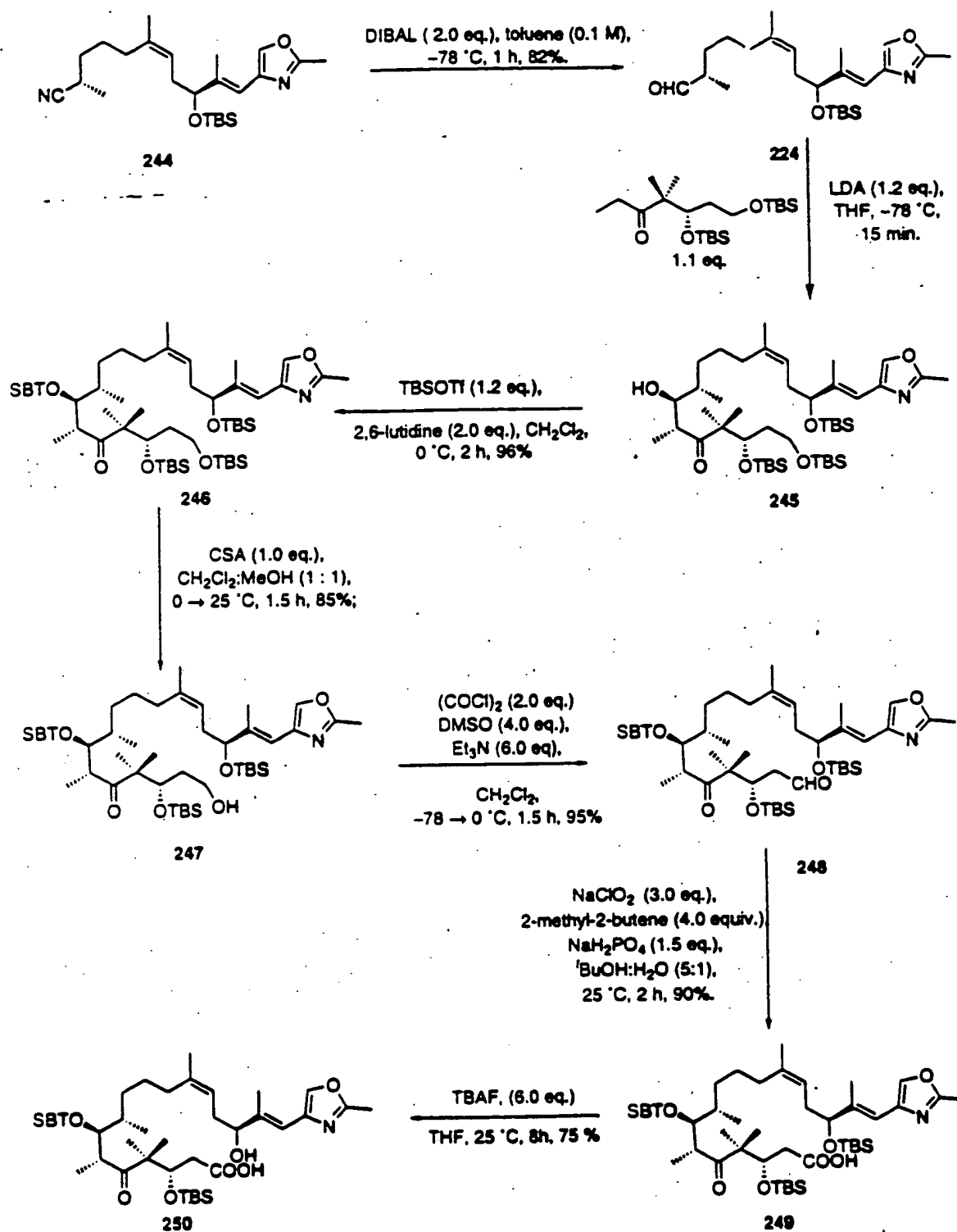


FIGURE 35

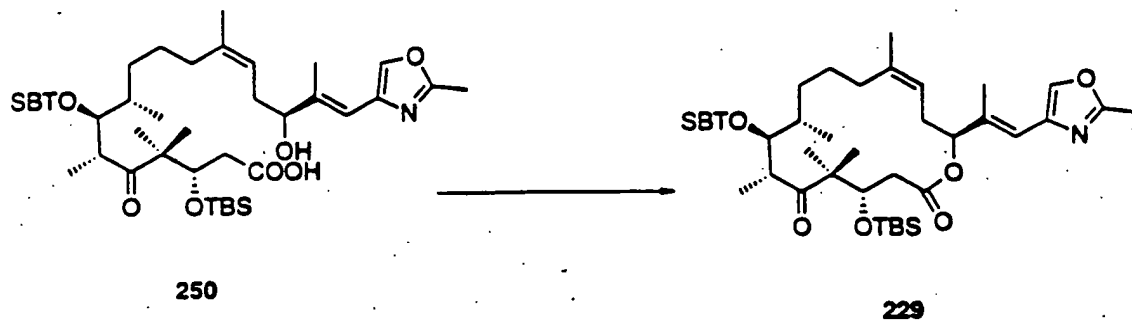


FIGURE 36

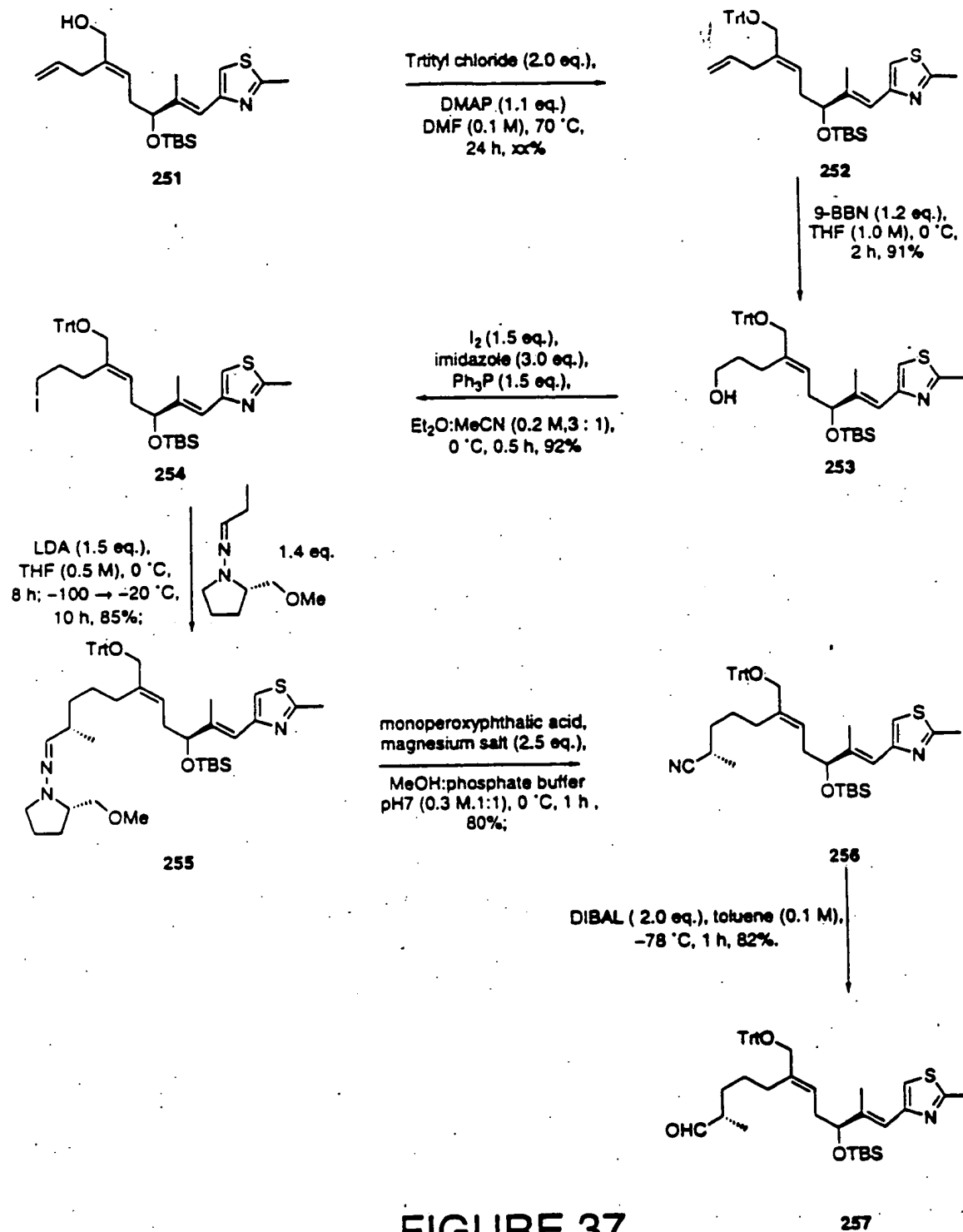


FIGURE 37

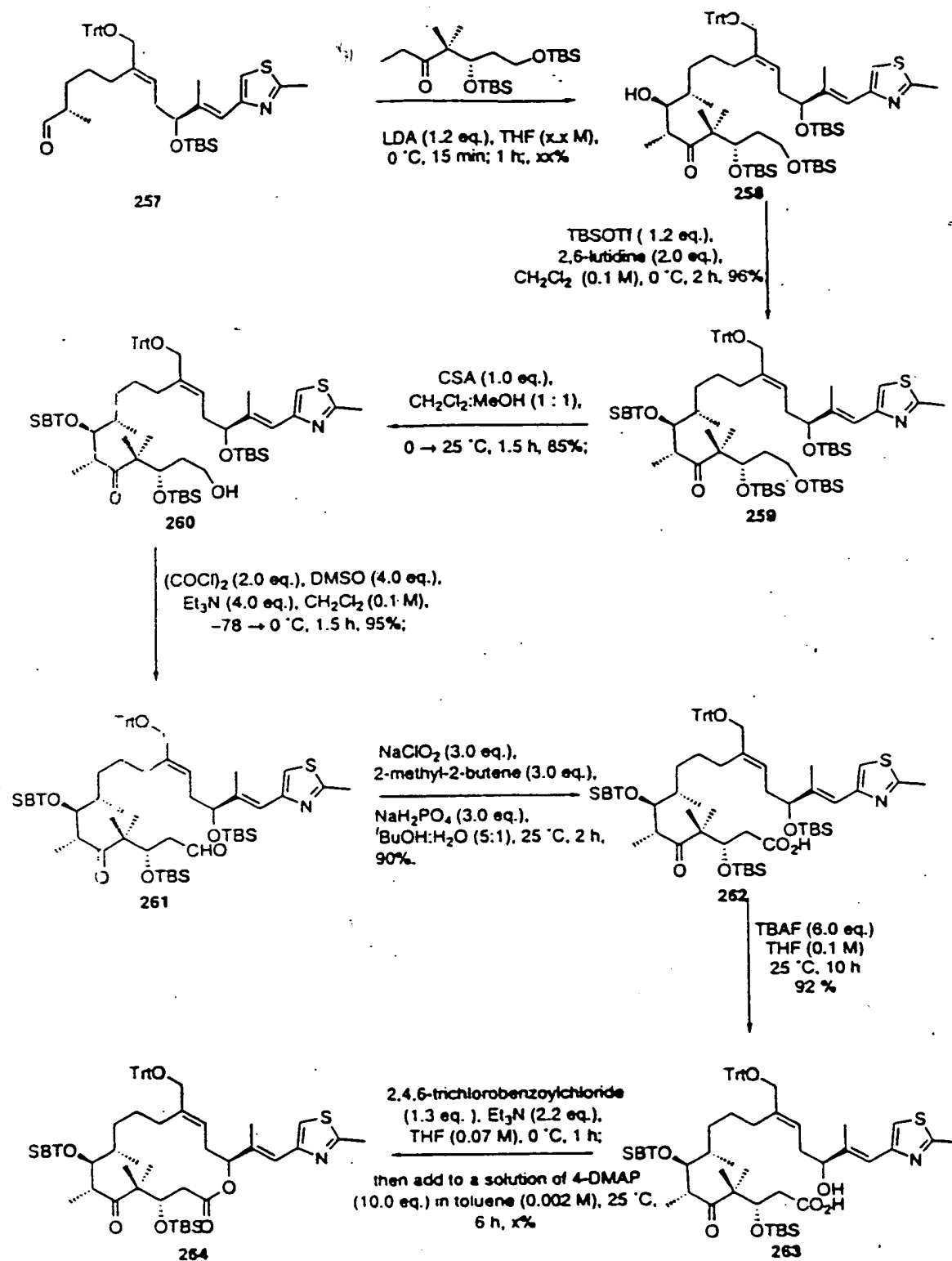


FIGURE 3E

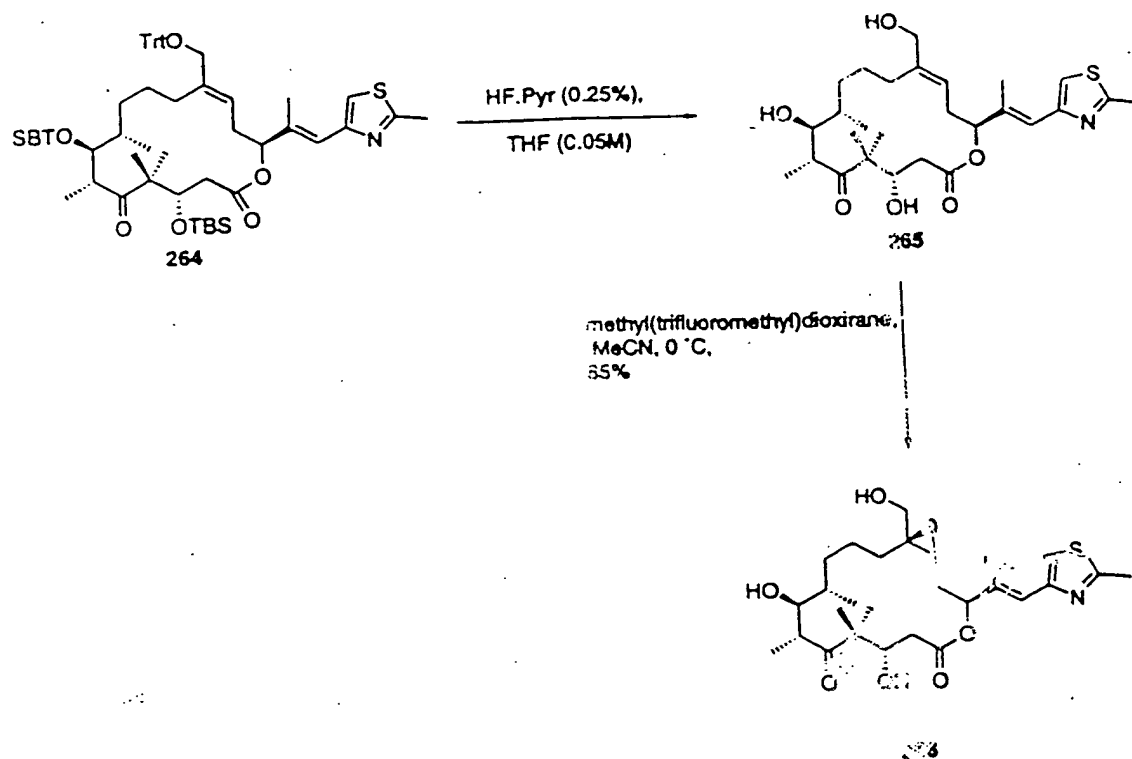


FIGURE 39